DAMAGE CONTROL ORTHOPAEDICS AND THE COGNITIVE EFFECTS OF CEREBRAL FAT EMBOLUS

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Declaration

This thesis represents research undertaken in the Department of Orthopaedic and Trauma Surgery, University of Edinburgh and has been composed by the author. The work is original, and is my own except where specifically acknowledged. It has not been submitted elsewhere in candidature for any other degree, diploma or qualification.

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Abstract

Introduction Trauma or surgery involving long bones can produce haemodynamic, embolic, coagulative and inflammatory changes. Patient outcome depends upon the initial response to injury and to subsequent medical and surgical intervention. 'Damage Control' surgery has been proposed in the initial care of seriously injured patients requiring stabilisation of extremity fractures. This involves initial external fracture fixation as opposed to intramedullary stabilisation in an effort to reduce surgical impact to the patient. Transcranial ultrasound techniques have detected cerebral emboli after long bone fracture stabilisation and joint arthroplasty. The clinical effects of these embolic events in terms of cognitive and cerebral dysfunction are unclear.

Hypothesis Orthopaedic long bone procedures produce measurable embolic, coagulative, inflammatory and clinical cognitive changes that affect patient outcome following surgery.

Studies This thesis consists of two clinical projects, a case report and a large animal (ovine) study. The large animal study consisted of an ovine model of severe musculoskeletal trauma under terminal anaesthesia. It involved the analysis of haemodynamic, pulmonary embolic, coagulative and inflammatory responses to bilateral femoral fractures and hypovolaemic shock comparing two different surgical strategies of fracture fixation (damage control versus early total care). This study aimed to better quantify the relative consequences of initial surgical management (external fixation versus intramedullary stabilisation) against a background of severe injury. Both

clinical projects involved the use of transcranial Doppler ultrasound monitoring of the cerebral circulation to quantify the cerebral embolic load, with detailed clinical cognitive testing and the measurement of a serum marker (S100B protein) of neuronal injury. The first study involved trauma patients requiring intramedullary stabilisation of femoral and tibial diaphyseal fractures and the second study examined patients undergoing primary lower limb arthroplasty. The primary aim of both studies was to accurately quantify cognitive change after surgery and to assess whether these measurements correlated with intraoperative cerebral embolic load and serum S100B protein concentrations following surgery. The case report (chapter 4) details the clinical history and cognitive follow-up of a survivor of fat embolus syndrome over an 18-month period.

Results The animal study demonstrated a higher pulmonary embolic load with early intramedullary femoral fracture fixation compared to external fixation. However, the initial fracture fixation method did not affect animal mortality or changes seen in the measured coagulation and inflammatory markers. Specific and quantifiable defects in cognitive function occurred after surgery in both clinical studies. However no direct correlation was found between cognitive change and cerebral emboli detection.

Conclusion Pulmonary and cerebral embolic events were detectable and quantifiable after elective and emergency orthopaedic procedures. Altering surgical technique can reduce the embolic load. However a linear correlation between embolic load and clinical outcome was not established.

Thesis Hypothesis

Orthopaedic long bone procedures produce measurable embolic, coagulative, inflammatory and clinical cognitive changes that affect patient outcome after surgery.

Chapter 1 Introduction

1.1 The Problem of Fat Embolus in Orthopaedic Surgery

Major trauma or surgery to a long bone may disturb the intramedullary canal and produce pressure and mechanical changes which result in the extravasation of fat and marrow into the venous circulation [1]. This embolic material circulates back through the heart and can enter the pulmonary circulation. Once there localised lung damage may occur by a combination of: 1. Mechanical obstruction of pulmonary arterioles to produce direct tissue hypoxia. 2. Chemical damage to the pulmonary parenchyma by lipase enzyme activation of benign fat into toxic free fatty acids [2].

The process of fat embolisation is most commonly described after skeletal and soft tissue trauma [3] but has a wider possible aetiology. It can occur following burns [4], osteomyelitis [5], pancreatitis [6], sickle cell disease [7] and decompression sickness [8]. Studies in patients undergoing fracture stabilisation or lower limb arthroplasty provide an opportunity to observe the effects of these common and usually benign pulmonary embolic events. However, occasionally fat emboli are associated with a more severe and systemic group of symptoms and signs. This is often attributed to emboli bypassing the protective filtering mechanism provided by the pulmonary microvasculature and directly entering the systemic circulation. Once there they can circulate to and affect the other end organs such as the brain, kidney, eye and skin. This process is complex and cannot be attributed solely to mechanical capillary blockage as the volume of fat embolus involved is small [9] and would be unable to cause the systemic upset which is

occasionally seen. It is likely that the pathogenesis of this syndrome involves a number of factors, which contribute to end-organ damage.

1.1.1 Definition and Diagnosis

Fat embolus is defined as fat within the circulation, which can occur with or without clinical sequelae. This occurs to a greater or lesser extent in all procedures, which disturb the intramedullary canal [1]. Tachakra and Sevitt confirmed that the majority of long bone fractures produce a mild and transient hypoxaemia detectable only on arterial blood gas analysis and pulse oximetry [10]. This is asymptomatic in the majority of cases and is attributed to fat and bone marrow embolic release at the time of injury or during subsequent stabilisation procedures.

Fat embolus syndrome (FES) in the context of orthopaedic and trauma surgery is defined by the production of specific systemic symptoms and signs which are associated with fat emboli. This syndrome is rare and occurs less frequently than fat embolus *per se*. Pulmonary fat emboli occur in most patients following major fractures but only a small number will develop clinical features of FES. This condition can develop immediately or in the days following injury. There is a wide range of possible clinical sequelae but the condition is generally characterised by dyspnoea, cerebral confusion and petechial haemorrhages which tend to affect the skin of the upper torso and conjunctiva.

The diagnosis of fat embolism syndrome (FES) was originally made on the basis of Gurd's and Wilson's criteria [3], (see Table 1) which consist of a combination of clinical, and laboratory findings. Major features included respiratory insufficiency, acute cerebral confusion and a petechial rash. Minor features included pyrexia, tachycardia,

retinal exudates, jaundice and renal dysfunction. Additional laboratory tests included anaemia, thrombocytopenia, high erythrocyte sedimentation rate and fat macroglobulaemia. One major criterion, four minor criteria and a finding of fat macroglobulaemia were required to give a definite diagnosis [11].

Table 1

Gurd's Criteria for Fat Embolus Syndrome (FES) [11]

Major Criteria

- Axillary or Subconjunctival petechiae
- Hypoxaemia ($PaO_2 < 60$ mmHg; $FiO_2 < 0.4$)
- Neurological depression out of proportion to hypoxaemia

Minor Criteria

- Tachycardia > 110 beats per minute
- Pyrexia > 38.5 °C
- Retinal emboli
- Renal Changes
- Acute haemoglobin drop
- Thrombocytopaenia
- Elevated ESR
- Fat macroglobulinaemia

In a double-blind therapeutic study examining the effects of methylprednisilone on FES after tibial fractures, Lindeque criticised Gurd's criteria and indicated that they may under diagnose the condition [12]. The diagnosis as described by Lindeque is based upon respiratory measurements and patients were only deemed to have the condition if one or more specific respiratory criteria were demonstratable. An increase in the diagnosis of FES was found following their application. These criteria included: a sustained arterial oxygen concentration of <8kPa with a fixed inspiratory oxygen concentration of 0.21 kPa; a sustained arterial carbon dioxide concentration of >7.3 kPa

or pH<7.3 (respiratory acidosis); Tachypnoea > 35 breaths per minute; increased work of breathing based on dyspnoea, use of accessory muscles, anxiety and tachycardia.

More recently the role of fat embolisation in the production of acute respiratory distress and multiple organ failure following injury has been examined. Acute respiratory distress syndrome (ARDS) is the term used to describe respiratory failure following high-energy trauma. This 'respiratory insufficiency' occurs against a background of multiple-organ (systemic) dysfunction. The terms, 'fat emboli', 'fat embolus syndrome' and 'acute respiratory distress syndrome' are often used interchangeably within orthopaedics. Although these conditions have considerable overlap (e.g. refractory hypoxaemia and pulmonary infiltration on chest radiograph) it has become recognised that ARDS should be considered as a distinct clinical entity. ARDS is considered to be at the most severe end of a spectrum of respiratory insufficiency that can follow injury. In 1994 an accurate definition of ARDS was given by the American and European Concensus Conference [13]. The diagnostic criteria for ARDS are shown below in table 2.

Table 2

American-European Concensus Conference definitions of Acute Respiratory Distress Syndrome [13]

ARDS Criteria
Acute Onset
PaO2/FiO2 < 200mmHg (26.7 kPa)
Bilateral infiltrates on an AP chest radiograph
Pulmonary artery occlusion pressure < 18 mmHg or no clinical evidence of left atrial hypertension

1.1.2 Incidence

The incidence of FES following long bone fractures is much lower than detectable fat embolus. A 10-year review by Bulger indicated an incidence of only 0.9% [14]. However higher figures have been reported with an incidence of up to 25% following isolated long bone trauma [4,15-17]. Mellor indicated that retrospective studies involving orthopaedic and trauma patients often reported a low incidence of FES with a higher incidence seen in prospective studies with the use of more objective measurements [18]. This variance may be due to a wide spectrum of disease existing with subtle forms of the condition being detected only on careful prospective monitoring and missed in retrospective analysis. In a prospective study performed by the Edinburgh trauma unit the rate of acute respiratory distress following blunt injury was 0.5% with a higher incidence seen in young patients following high energy injuries [19]. The incidence of complications related to fat emboli and respiratory insufficiency after trauma has decreased over the years due to improvements in fracture management and resuscitation.

The level of trauma has been shown to correlate with the incidence of fat embolus syndrome with a higher incidence in multiple fractures [17,20]. Robert reported an incidence of FES of 0.26% with a mortality rate of 20% correlating to higher injury severity scores [20]. In a prospective study, Chan reported an incidence of FES of 8.75% in a group of fracture patients. This incidence rose to 35% in patients who had sustained multiple fractures. 64% of patients in the entire cohort had hypoxaemia and 52% demonstrated fat globules in the peripheral venous circulation. The 'iceberg' phenomenon of fat embolism syndrome was suggested and describes possible sub-clinical and less severe forms of this condition.

Associated injuries may also mask the clinical features of FES and make specific diagnosis more difficult. Separating prognostic factors related to FES from those simply related to injury severity can be difficult.

1.1.3 Clinical Features

The early diagnosis of developing symptoms and signs related to fat embolus release is important to instigate early supportive treatment. However, the possible clinical indicators and laboratory investigations are not universal, consistent or specific to the condition. There is no specific test available to diagnose FES or ARDS. The major and minor criteria described by Gurd [11] (see table 1 on page 11) in relation to FES are non-specific and overlap with other features of injury unrelated to fat embolus release.

Respiratory involvement with hypoxia is the most common finding and usually develops 12-48 hours after injury [2,21]. Gurd indicated that 75% of his original 100 FES patients had predominant respiratory signs [22]. Bulger demonstrated acute hypoxia in 96% of patients [14]. However, FES can be a diagnosis of exclusion only made once other causes of hypoxia (e.g. pulmonary contusion, pneumothorax, pneumonia and pulmonary thromboembolus) have been excluded. Therefore, in an injured patient hypoxia *per se* is not specific to FES. The condition is characterised by hypoxaemia resistant to oxygen therapy (i.e. refractory hypoxaemia).

This may explain the reported, relatively high incidence of FES which follows isolated long bone fractures where detectable hypoxaemia is common [10]. In more seriously injured patients, associated injuries may mask the contribution of FES to developing respiratory distress.

The common pulmonary features of FES and ARDS include dyspnoea with an associated hypoxaemia, which is refractory to oxygen therapy. Haemoptysis has also been described. Chest radiographs classically show areas of patchy consolidation [4]. In the initial stages, hyperventilation and dyspnoea produces a low arterial PCO2 concentration against a background of hypoxaemia. However as the disease progresses and with increasing respiratory distress the PCO2 levels rise and respiratory and metabolic acidosis combine. Hypoxaemia is dependant upon the administration of oxygen and therefore the degree of respiratory insufficiency is calculated by the ratio of arterial oxygen concentration (PaO2) over the fraction of inspired oxygen being administered (FiO2). As previously indicated a ratio of less than 26.7 is required for the specific diagnosis of ARDS.

However, there does appear to be a spectrum of respiratory compromise of which the patient with fulminant FES or ARDS represents only the most severe end. One indicator of this is that the incidence of mechanical ventilation during periods of respiratory distress secondary to fat embolus release tends to vary greatly. Ganong reported a 0% usage of mechanical ventilation with a FES incidence of 26% in young skiers who had sustained an isolated long bone fracture to the tibia or femur [16]. Morbidity appeared minimal with only 50% having a delayed hospital discharge as a result of this fracture complication. However, in a 10 year retrospective review of long bone fractures in a level-one trauma centre, Bulger reported an incidence of FES of only 0.9% but with a higher incidence of serious clinical sequelae and a 44% usage of intubation and mechanical ventilation [14]. This discrepancy in the incidence and severity of the condition is likely to be due to reporting of arterial hypoxaemia. As previously

indicated this is common finding after isolated long bone fractures with an incidence of around 60% [10,17,23] which increases with multiple fractures.

The petechial haemorrhages described in FES are commonly found in the upper torso and conjunctiva. This distribution is thought to result from fat embolisation to areas of skin supplied by the carotid and subclavian vessels, with associated endothelial damage and localised coagulation resulting in haemorrhage. Although the skin changes are pathognomic of the condition they are not present in all cases and have a reported incidence of around 60% [22,24]. The skin lesions vary in intensity and can be difficult to visualise with the naked eye. This could account for lower incidences seen in retrospective studies with lower sensitivities of reporting [14]. Retinal haemorrhages with intra-arterial fat globules have been reported on fundoscopic examination, with a reported incidence of around 60% [22]. However, this investigation is often not carried out routinely on patients with diagnosed FES [14].

Documented cerebral manifestations of fat embolus syndrome are variable and non-specific and have a reported incidence of around 80% [22]. They include acute confusion, headache, lethargy, irritability, stupor, seizures, stroke and coma [25,26]. The possible aetiology of neurological dysfunction has been debated and includes hypoxaemia secondary to emboli in the pulmonary circulation [27,28] and intracranial hypertension resulting in cerebral oedema (detectable on MRI imaging) [29,30]. In addition, mechanical and chemical theories of cerebral injury have been proposed. Paradoxical fat embolisation through the cerebral circulation could result in transient ischaemia owing to small arteriole or capillary occlusion. Perivascular oedema could also be caused by cerebral damage caused by the metabolism of benign fat to toxic free fatty acids. It is

likely that a combination of processes are involved and it should be noted that cerebral manifestations can occur in the absence of hypoxaemia with little pulmonary involvement [31].

Enhanced imaging techniques such as MRI can aid the early clinical diagnosis of FES with nonconfluent areas, a restricted diffusion pattern and oedematous changes indicating multiple cerebral micro-emboli with no clinical history of cranial trauma [32]. These images have been shown to be a sensitive and consistent method of diagnosing early cerebral fat embolus with evidence of acute cerebral microinfarctions. However, these more detailed but often less available investigations tend to be used when the diagnosis and aetiology are unclear (e.g. with an associated head injury). An alternative diagnostic method has involved the use of transcranial Doppler sonography [33]. Transcranial Doppler has been used to quantify cerebral microemboli in patients undergoing open cardiac and carotid surgery as well as those medical patients at risk of embolic stroke. However, this technique has also recently revealed both cerebral fat embolic events and decreased cerebral blood flow during the acute stage of FES in trauma and elective orthopaedic patients undergoing potentially emboligenic surgical procedures [34,35]. This non-invasive method of investigation has the potential to be used as a useful intraoperative monitoring tool.

Generalised global and transient cerebral dysfunction appears to be a common clinical finding with FES [18]. However, the long-term cognitive effects of this condition are unclear and there is little documented evidence using detailed cognitive testing. Richards [36] indicated that patients who have experienced cerebral fat emboli may exhibit sub-clinical symptoms and signs, which are being missed in the standard ward

environment. Commonly used, standard cognitive ward tests such as the Glasgow Coma Scale [37] and Mini-Mental State examination [38] could lack the sensitivity required to detect subtle cognitive change. Similar to respiratory compromise, which follows pulmonary fat embolism, the acute and apparently transient effects of cerebral fat emboli may represent one aspect of a wider spectrum of neurological and cognitive compromise. The immediate and long-term cognitive effects of cerebral fat emboli generated by orthopaedic procedures in patients with no direct neurological injury are currently poorly defined.

1.1.4 Pathophysiology

There are 2 main theories as to the pathogenesis of respiratory and systemic symptoms related to fat embolus: mechanical and biochemical.

The mechanical theory states that fat globules are forced into the venous circulation owing to pressure changes in the medullary canal and circulate into the pulmonary circulation where they obstruct small arterioles and capillaries. Direct mechanical obstruction of the pulmonary microvasculature may therefore contribute towards the hypoxaemia commonly detected [10]. A patent foramen ovale or transpulmonary artero-venous shunt are thought to predispose the condition by allowing emboli to bypass the pulmonary filtration process, enter the systemic circulation and produce similar direct mechanical affects on other end-organs such as the kidney and brain [1,28,39-41]. Surgical procedures involving instrumentation of the medullary cavity are associated with increased intramedullary pressures and fat embolus production [42-44]. Instrument design and surgical techniques have concentrated on reducing the

intramedullary pressure and intramedullary fat content as methods of reducing the volume of fat embolus released [42].

The biochemical theory is based upon the end products of fat emboli causing toxicity and damage to the capillary endothelial lining of end organs. Benign fat is converted to a more toxic free fatty acid form by lipase enzymes or catecholamines produced after injury, surgery or illness which cause toxic pneumocyte damage [2]. In addition chemical mediators released by trauma are thought to stimulate fat coalescence by altering blood lipid solubility and predisposing to embolisation [4]. This may offer an explanation for non-traumatic forms of FES and the delay seen between a precipitating event and the development of clinical features of the condition.

The stimulation of coagulative processes combined with hypovolaemia may also cause circulatory compromise, platelet aggregation and contribute towards the systemic nature of this condition [45]. In addition there has been much recent interest in the potential imbalance between the systemic inflammatory reponse (SIRS) and compensatory antiinflammatory response (CARS) which occurs following trauma [46]. This has the potential to produce respiratory and other end-organ damage. ARDS is thought to represent a localised (pulmonary) form of this systemic inflammatory imbalance with pathophysiological features, which involve an outpouring of inflammatory exudate into the pulmonary interstitaial fluid with subsequent fibrosis and damage to the Type 1 pneumocytes, which form an integral part of the alveolar/capillary basement membrane.

It is most likely that the clinical features caused by fat embolisation are a combination of the above processes. Aoki at al studied 20 patients undergoing reamed

intramedullary fixation for femoral and tibial diaphyseal fractures of which 5 had fat embolus syndrome defined by clinical features [47]. Using transoesophageal ultrasound and alveolar lavage techniques a direct relationship between the amount of echogenic material entering the pulmonary circulation and the proportion of lipid-laden cells in the aspirated alveolar lavage samples was demonstrated. However, the 5 FES patients had significantly higher lavage leucocyte counts and albumin concentrations but with no corresponding increase in the degree of echogenicity seen on ultrasound. They concluded that factors other than direct mechanical obstruction such as inflammation and neutrophil migration contributed towards the development of this condition.

Transpulmonary passage of embolic particles through the pulmonary microvasculature has also been demonstrated. The pulmonary microvasculature acts as a filter to fat macroglobules with larger particles blocking the lung capillary bed and smaller particles (< 7-10 μm in diameter), being able to pass through and enter the systemic circulation [2]. Byrick demonstrated the trans-pulmonary passage and deformable nature of fat using a large animal model of bilateral cemented hip arthroplasty. Increases in pulmonary arterial pressure forced fat particles further into the smaller and more distal vessels of the pulmonary capillary tree [39]. The analysis of end organs (brain, kidney and heart) three hours after bilateral cemented arthroplasty demonstrated evidence of intravascular fat in all tissues. No patent foramen ovale was found in any animal. Transpulmonary passage of micro-emboli is possible, but with a significant embolic load and under high pressure conditions.

In orthopaedic trauma it has not been possible to measure pressure changes during fracture, however increases during intramedullary nailing procedures have been

accurately measured and a close correlation established with the degree of fat intravasation [42]. The normal intramedullary pressure is around 30-50mm Hg (4-6.7kPa) [2]. Pressure increases of up to 1000 mmHg (130kPa) have been observed as a consequence of intramedullary procedures involved in long bone stabilisation techniques [42]. By modifying reaming design and technique Mousavi demonstrated reduced transcardiac embolic signals on transoesophageal echocardiography [42].

1.1.5 Predisposing Factors

The screening of trauma patients to identify those 'at risk' of developing respiratory insufficiency and symptoms related to fat embolus is key to the early diagnosis and treatment of the condition. Following long bone injury, males under the age of 30 with significant and early hypoxaemia are considered to be at a higher risk of developing FES, emphasising respiratory insufficiency as a key concept of the condition [48]. Age may be a factor in the development of symptoms related to fat embolus. In a consecutive series of 274 patients with isolated femoral shaft fractures, Pinney showed a 4% incidence of FES [49]. There were no cases in patients aged over 35 years. The risk of developing FES was also reduced by early intramedullary fracture stabilisation within 10 hours of admission. All 11 cases of FES in this study occurred in patients aged under the age of 35 years who had delayed (> 10 hours) femoral fracture stabilisation. It was concluded that in patients under the age of 35 femoral diaphysial fixations should be performed as early as possible.

The incidence of FES and acute respiratory distress is highest after trauma and in particular lower limb fractures. In a large prospective study of 7192 trauma patients requiring hospital admission White et al used multiple logistic regression analysis to

demonstrate several independent predictors for the subsequent development of acute respiratory distress [19]. These included a young age, Injury Severity Score, the presence of a femoral fracture, the combination of abdominal and extremity injuries and physiological compromise on admission. Fracture and injury patterns appear to alter the incidence of FES. The injury severity score and presence of a femoral fracture have been linked to the development of FES and respiratory distress after injury with higher incidences seen in more severely injured patients [20,50]. The condition is also more common with lower limb and multiple fractures [4]. Increasing levels of trauma especially to the chest, head and abdomen have been associated with higher incidences of symptoms related to fat embolus such as respiratory distress [19]. Open fractures have been described as having a lower incidence [51] with the decompressive effect on the intramedullary canal with an open fracture possibly reducing the amount of embolus released and entering the venous circulation.

The time from injury also appears to be a key factor in the development of this condition. In a prospective study of 136 patients who had sustained pelvic, femoral or tibial fractures, the peak incidence of fat macroglobulemia occurred within eight hours of injury in those patients with corresponding clinical signs related to fat embolus (dyspnoea, confusion and petichial haemorrhages) [50].

Fat, bone marrow or air may enter the systemic circulation via a patent foramen ovale in the heart or through arterial-venous shunts in the pulmonary circulation. The reported incidence of a patent foramen ovale using transoesophageal echocardiography and the Valsalva manoeuvre is around 20% [52]. Patients with a patent foramen ovale have been reported as having a predisposition to the systemic effects of fat emboli due to the

bypassing of the protective filtration mechanism provided by the pulmonary circulation and a subsequent higher systemic embolic load [40]. Paradoxical embolisation through arterial-venous shunts in the pulmonary circulation has also been shown to occur during lower limb arthroplasty [28]. The quantity of embolic material detected in the cerebral circulation using transcranial Doppler ultrasound being correlated to the shunt size.

The incidence of artereo-venous pulmonary shunting after fracture has previously been described [53]. In a consecutive study of 92 patients with long bone and pelvic fractures approximately 50% had a pulmonary shunt indicated by a large alveolar/arterial oxygen concentration gradient [53]. The majority (80%) of these patients with a detectable artereo-venous shunt following fracture had an associated chest injury. This altered pattern of pulmonary circulation may provide an explanation for increased rates of systemic complications related to fat emboli reported in fracture cohorts with associated chest trauma.

A key factor in the development of symptoms related to fat embolus following femoral or other lower limb long bone fractures appears to be the volume of embolic material released from the fracture site during fracture stabilisation procedures. In 110 patients who underwent reamed intramedullary nailing of femoral and tibial fractures Christie et al demonstrated that the majority had detectable embolic events on transoesophageal echocardiography [1]. A correlation was established between embolic intensity and measured pulmonary responses. Patients with reamed pathological fractures sustained the highest measured pulmonary embolic load and subsequent post-operative mortality rate (21%). Post mortem analysis revealed immature bone and clot with extensive pulmonary thromboembolism. One patient who had a patent foramen

ovale exhibited widespread systemic end-organ embolisation on post mortem analysis. The degree of cardiorespiratory reserve has been suggested as a key determinant on a patients ability to cope with these intraoperative pulmonary embolic events [54]. As previously stated Aoiki demonstrated highly echogenic material passing though the heart and into the pulmonary circulation following reamed intramedullary nailing [47]. The degree of echogenicity correlated to the percentage of lipid-laden cells in broncho-alveolar lavage samples, but not to clinical sequelae in terms of fat embolus syndrome. Factors other than the degree of pulmonary microvasculature obstruction were thought to be involved with the 5 FES patients showing higher lavage albumin concentrations and leukocyte counts.

1.1.6 Fat Embolus and Lower Limb Arthroplasty

The condition was described in 1970 as a result of a cardiac arrest during a cemented hip arthroplasty [55]. Hypotension, hypoxaemia and cardiac arrest are possible complications that have been attributed to fat embolus release during lower limb arthroplasty. In a large retrospective review of intraoperative mortality during hip arthroplasty over a 28 year period Parvizi described a FES incidence of 0.1% [56]. All deaths occurred during cemented arthroplasty and were attributed to irreversible cardiorespiratory disturbances. Post mortem pulmonary tissue analysis of 13 patients revealed the presence of bone marrow microemboli (11 patients) and methylmethacrylate crystals (3 patients). Improvements in surgical technique to reduce the fat embolic load released from the femoral intramedullary canal were attributed to marked reductions in intra-operative mortality seen towards the end of this study. Fat embolisation during hip arthroplasty can be caused by the high intramedullary pressures

generated with cement pressurisation and femoral stem insertion. However there are reports of cases and fatalities occurring in uncemented procedures [57].

Increased femoral intramedullary canal pressure has been consistently shown during cement pressurisation and femoral stem positioning in the medullary cavity with the resultant intravasation of emboli into the venous circulation [58]. Adequate preparation of the femoral canal prior to insertion of the cement restrictor and cement pressurisation is essential in minimising the pulmonary embolic load. Breusch et al [59] demonstrated using a large animal (ovine) model that improved intramedullary lavage techniques (i.e. pulsatile lavage) resulted in a substantial reduction in fat embolus release during femoral component cementation. A prospective clinical study of 24 cemented hip hemiathroplasty cases concluded that inadequate methods of femoral canal lavage were attributable to higher detectable pulmonary embolic loads detectable on Transoesophageal echocardiography (TOE) and greater changes in measured cardorespiratory parameters [60]. Distal femoral canal venting has also been shown to reduce intramedullary pressure and subsequent emboli production [58].

Transoesophageal echocardiography (TOE) is a specific and sensitive method of detecting pulmonary embolism during lower limb arthroplasty and can allow the instigation of early supportive treatment [61]. It has been suggested that more invasive methods of monitoring such as TOE may be indicated in patients undergoing cemented hip arthroplasty who have evidence of cardiopulmonary compromise [61]. However this type of monitoring is not universally available and has a small but documented morbidity and mortality risk due to oesophageal perforation during endoscope insertion [1].

Knee arthroplasty can result in fat embolus syndrome with a combination of both cardiorespiratory and cerebral clinical symptoms and signs [62]. A prospective comparison of 100 unilateral versus 100 bilateral knee replacements demonstrated an incidence of FES of 3%, with 4 out of the 6 affected patients having had a bilateral procedure [27]. This study demonstrated an incidence of fat embolism detected in blood sample analysis using an oil red O fat stain of 46% in the unilateral and 61% in the bilateral cohort. Similar to intramedullary fracture fixation the production of fat emboli is common after knee arthroplasty but rarely symptomatic.

Bilateral knee arthroplasty has been shown to produce greater incidences of postoperative confusion and cardiorespiratory problems. Lane et al [63] prospectively compared 100 unilateral and 100 bilateral procedures and found that the confusion rate after surgery was four times higher in the bilateral group (29% versus 7%). This was thought to be due to an increased incidence of fat embolism as other potential factors such as analgesia, electrolyte imbalance, hypoxaemia and anaemia were similar in both groups. Cardiorespiratory problems were three times commoner in the bilateral group (15% versus 5%) possibly indicating a greater pulmonary embolic load with the bilateral procedure. However in a similar study of unilateral versus bilateral hip arthroplasty using cemented and uncemented stems, no significant difference in the prevalence of detectable fat emboli was seen [27].

During knee arthroplasty the intramedullary pressure with placement of the femoral intramedullary guide can markedly increase [64]. A positive correlation was made between this pressure increase and the degree of arterial to venous pulmonary shunting

detected using arterial blood gas analysis. Cementation and pressurization of the tibial components has also been associated with a fat embolic shower and this was again more prevalent during simultaneous bilateral procedures [63].

Tourniquet release at the end of the procedure has been implicated in the detection of pulmonary embolic events. Kato [65] demonstrated a 100% incidence of pulmonary emboli detected by transoesophageal echocardiography after tourniquet deflation with cemented knee arthroplasty. However around 50% of patients in a subgroup with no tourniquet had detectable pulmonary embolic events with corresponding hypoxaemia related to the size of the embolic load. 27% of all patients' demonstrated significant pulmonary embolic events during femoral reaming whist the tourniquet were inflated. This indicated that an inflated tourniquet does not abolish all embolic events. On deflation of the tourniquet, the documented duration of these embolic events has been shown to last from 3-15 minutes with a peak intensity at 25-45 seconds [66]. A rise in mean pulmonary arterial pressure and fall in mixed venous oxygen concentration was observed. The size of the embolic material visualised was correlated to the degree of pulmonary vascular dysfunction with particles greater than 0.5 cm causing a significant rise in the pulmonary vascular resistance index. Three patients developed fat embolus symptoms with all three demonstrating pulmonary embolic material greater than 0.5 cm in size.

1.1.7 Cerebral (Systemic) Emboli

Transcranial Doppler ultrasound has been used to detect cerebral (systemic) emboli after intramedullary fracture stabilisation [34] and during lower limb arthroplasty [28,35]. Edmonds [35] demonstrated detectable cerebral emboli in 8 out of 20 patients

undergoing primary hip arthroplasty with a range of embolic signals from 1-200. These systemic embolic events occurred predominantly during impaction of the cemented femoral component and on relocating the hip prosthesis, but were occasionally detected during insertion of the cemented acetebular component. The clinical significance was unclear, as cognitive function was not formally assessed. However none of the 20 patients exhibited obvious clinical confusion after surgery and it was concluded that the cerebral embolic events were well tolerated. Riding [28] et al monitored 41 primary hip and knee arthroplasty patients of whom 34 had a pulmonary arterial-venous shunt. Cerebral embolic events were detected in 18 of these 34 patients and the degree of paradoxical systemic embolisation was correlated with pulmonary arterial-venous shunt size. A relatively high systemic embolic load was detected in two patients with one developing acute confusion and the other pancreatitis.

Cerebral embolic events have been recently measured after long bone fractures using transcranial Doppler techniques [34]. Forteza studied five trauma patients each of whom had clinical fat embolus syndrome. Transient cerebral embolic events were detected up to four days following intramedullary long bone fracture stabilisation. Time decay was demonstrable with more cerebral emboli detectable closer to the time of injury. Intra-operative monitoring also indicated that the number of embolic signals increased during intramedullary nail insertion [34]. All five patients had detectable systemic emboli but only one had a patent foramen ovale or demonstrable form of pulmonary artereo-venous shunting. In this patient larger and more prevalent embolic signals were detectable and the documented neurological sequelae more severe. However this patient had also received the most severe pattern of injury. The

preliminary results on a subsequent prospective evaluation of adult femoral fractures did correlate neurological symptoms with the number of embolic signals detected [67]. However, the extent to which these embolic events are correlated with defects in higher cerebral function in trauma patients remains unclear with direct cerebral injury and metabolic derangements often confusing the clinical cognitive assessment.

Cerebral embolic load has been correlated to the degree of cognitive dysfunction, which follows cardiopulmonary bypass surgery where neuropsychological deficits are common. A longitudinal study of cognitive function after coronary artery bypass surgery indicated that overall neuropsychological scoring declined at six days, but showed some recovery at eight weeks, though a relative dysfunction was still detectable at five years [68]. The intra-operative cerebral embolic load, short-term cognitive changes and the degree of recovery at eight weeks after surgery were identified as predictors of relative cognitive deficit at five years.

Arterial filters have been used to reduce the cerebral embolic load and help prevent cognitive dysfunction. Pugsley et al studied 100 patients undergoing cardiopulmonary bypass surgery and randomized 50 of these patients into receiving an arterial line filter [69]. Neuropsychological sequelae were found to be more common in the non-filtered group with a positive correlation made between cognitive dysfunction at eight weeks after surgery and the number of intra-operative embolic signals detected using transcranial Doppler ultrasound monitoring of the middle cerebral artery. In addition a group of patients exhibiting 'soft' neurological signs in the non-filtered group were identified.

A broad range of cognitive dysfunction may exist after trauma or major surgical procedures with acute confusion, stroke and coma representing only the severe end of a spectrum of cognitive compromise. Detection rates of cerebral embolic signals after trauma and intramedullary orthopaedic procedures appear to be higher than the incidence of clinically detectable neurological sequelae. The insensitive nature of commonly used cognitive testing methods such as the Glasgow Coma Scale and Mini-Mental State Examination may offer an explanation. Most cases of cerebral fat embolisation are thought to be transient and resolve quickly. However more subtle signs such as visual disturbances and personality changes have been described [22,70] indicating that there may be a broader spectrum of cognitive compromise other than the acute and obvious features of delirium and coma that are often described and associated with the condition. Accurate descriptions of cognitive and central nervous dysfunction experienced by patients after major orthopaedic procedures that produce fat embolic events are scarce. Accurate correlations have not been established between cognitive function and the cerebral embolic load detectable with available transcranial Doppler monitoring techniques.

1.2 The Assessment of Cognitive Function and Cerebral Injury after Orthopaedic Surgery

1.2.1 Previous Research

Acute confusion or delirium has defined diagnostic criteria taken in accordance with the American Psychiatric Association (DSM-IV 1994) [71]. These criteria include: disturbance in consciousness (reduced ability to focus, sustain or shift attention); change in cognition (memory impairment, disorientation or language disturbance) or perceptual disturbance (misinterpretations, illusions, hallucinations). Such changes should have developed over a short period of time and can vary over the course of a day. In addition laboratory or clinical evidence should exist to indicate that the delirium state is directly caused by the physiological disturbances produced by a medical condition.

Acute confusion after surgery is a common problem and has a close correlation with morbidity and mortality [72]. It can occur for a variety of reasons. Risk factors include: age, hospitalisation, duration of anaesthesia, respiratory complications and infection after surgery with other causative factors including hypoxaemia and hypotension [73]. Cognitive impairment after cardiopulmonary bypass surgery is well recognised and the causative factors have long been a topic of debate. The two commonest causes of operation-related cognitive decline in this area are hypoperfusion or an embolic stroke. The reported incidence varies greatly and depends upon the clinical criteria and the timing of assessment after surgery [74].

Cognitive dysfunction has been well recognised after hip fracture. In a comprehensive review of the available literature Bitsch identified an incidence of acute delirium after surgery of 35% [75]. The only risk factors showing a strong correlation to

the development confusion were age and pre-existing dementia. The pathophysiology behind this process remains unclear. Gustafen demonstrated in 111 fractured neck-of-femur patients, an incidence of acute confusion after surgery of 61% with resulting higher complication rates and a prolonged hospital stay [76].

In the hip fracture studies reviewed by Bitsch [75], the three commonly used tools for cognitive assessment were: Mini-Mental State Examination (MMSE) [38]; confusion assessment method (CAM); organic brain syndrome scale (OBS) [77]. These are used to recognise the main features of delirium and are applicable with some clinical experience in the ward environment. An accurate pre-operative assessment is required to obtain a baseline value for comparison with tests performed after surgery [78].

The use of the above tests as sensitive indicators of cognitive dysfunction after joint arthroplasty or long bone fractures requiring intramedullary stabilisation is less established. Three studies, which evaluated cognitive function after hip surgery have all shown a reduced incidence of acute confusion after elective hip replacement, compared to acute hip fracture. Duppilis [79] used the MMSE to examine 149 acute hip fracture and 76 elective primary hip arthroplasty patients all of whom were over 65 years of age and cognitively intact prior to admission [79]. The overall incidence of post-operative acute confusion was 20% with a reduced incidence following hip arthroplasty (11.7%) compared to the fracture cohort (24.3%). Age and social isolation after hospital admission were linked to increased confusion risk.

This incidence corresponds with studies by Clayer [80] and Galanakis [81] which related age, pre-operative cognitive impairment, hyponatraemia, and hypoxia to the development of acute delirium. Clayer demonstrated that acute hip fractures had a

higher incidence of pre-operative cognitive dysfunction compared to age-matched elective hip arthroplasty patients and found that hypoxia in the fracture group was more prevalent [80]. Galanakis prospectively analysed over 100 patients undergoing elective hip arthroplasty or surgery for an acute hip fracture and used the Confusion Assessment Method (CAM) of cognitive assessment. Acute confusion was found to be most prevalent between days two and five with a higher rate in the fracture cohort of 40.5% compared to 14.7% following elective hip arthroplasty.

Clinical studies evaluating cognitive function after long bone diaphysial fractures have concentrated on patients with an associated head injury. Starr [82] concluded in 32 patients with a femoral shaft fracture and associated head injury, that early femoral fracture stabilisation did not increase the prevalence of post-operative neurological complications. The outcome measures of this retrospective study were deterioration in Glasgow Coma Scale, increase in the intracranial pressure and changes seen on head CT scanning. McKee [83] evaluated whether early intramedullary stabilisation (with its potential to generate cerebral embolic events) affected neurological outcome in the multiply injured patient with a closed head injury. Sensitive neuropsychological testing methods were used (Colour Trails A&B [84]). However follow-up was poor with only 30% of patients being cognitively evaluated. No form of transcranial monitoring was used to quantify the cerebral embolic load generated by the intramedullary femoral fixation. Their conclusion on evaluation of 10 patients was that cognitive function was unaffected by potential systemic emboli produced by intramedullary fixation.

The cognitive effects of an isolated long bone fracture with subsequent surgical stabilisation using available detailed cognitive tests suitable for a young patient population have not been performed. Previous studies which have detected cerebral embolic events have not formally measured cognitive function [34]. Other research has evaluated the more severely injured patient with associated chest and head injuries. In this type of patient there is uncertainty as to the aetiology of cognitive dysfunction between the direct effects of head trauma and indirect effects of cerebral emboli generated from the fracture site. Therefore a correlation between cerebral embolic events detectable using recently available transcranial Doppler ultrasound monitoring and cognitive clinical function has not yet been established.

1.2.2 Directions for Future Research

One concern over the assessment of cognitive function after surgery has been the relatively insensitive nature of traditionally applied ward tests such as the Glasgow Coma Scale and Mini-Mental State Examination. This could result in subtle changes in cognitive function being overlooked [36]. A wide variety of sensitive and validated neuropsychological tests are available to measure objectively a range of mental processes from memory testing to the performance of simple and more complex motor tasks [84-88]. Such tests have rarely been applied to orthopaedic patients. The key to an accurate assessment of cognitive function is to apply a wide range of clinical tests and assess patterns of performance within patient groups. The cognitive test scores obtained after surgery can be compared with pre-operative assessments or with predicted pre-morbid scores matched for age, sex and intelligence.

In addition, an increasing effort has been made to find surrogate markers for cerebral injury caused by trauma and ischaemia. Proteins expressed in the cerebrum can be released into the cerebrospinal fluid and can enter the systemic circulation to be detected by serum analysis. S100B protein is a calcium binding astroglial protein which is abundant within the central nervous system and is one of a range of possible protein markers of neuronal injury. This marker has been used to assess the degree of cerebral injury following surgical procedures involving cardiopulmonary bypass. Correlations have been established between S100B protein levels and cerebral microemboli as well as with the duration of bypass surgery [89]. Trends were also established between neurocognitive deterioration and increased post-operative S100B levels in cardiac patients. Cognitive dysfunction following cardiac bypass surgery is commonplace with a reported incidence of up to 70%. In a study of 64 cardiac surgical patients a positive correlation was found between increased serum levels of S100B protein and cognitive dysfunction [90].

Protein S100B has also been used successfully after acute ischemic stroke with respect to the neurovascular status. In a study of 32 patients admitted with an acute ischaemic stroke, increased levels of S100B protein were found to correlate with the volume of infarcted cerebrum determined by transcranial duplex sonography and the corresponding neurological deficit [91]. S100B levels have also been shown to correlate with the degree of middle cerebral artery occlusion and a more severe course of acute cerebral ischaemic disease [92]. The timing of sampling is also important. Jonsson [93] at al studied this with sequential blood samples in 56 patients undergoing cardiac surgery and

found that S100B level at one hour after surgery had a strong correlation to post operative cognitive dysfunction.

However, the specificity and sensitivity of this marker has been questioned. Contamination by extracerebral tissues either from damage or infection has produced false positive results and may be a limitation of this neuronal injury marker. Possible extracerebral origins of S100B protein include traumatized fat, muscle and bone marrow. In a prospective study of polytrauma patients without head injury compared to healthy volunteers, S100B protein levels were found to be well above the normal reference range in the injured cohort [94]. Patients with long bone fractures, burns and thoracic contusions produced the highest protein levels and it was concluded that the interpretation of S100B protein results after injury may be complicated by release from extracerebral tissues. Increased levels detected at 30-120 minutes following bilateral femoral fractures in a small animal model indicated that bone marrow is a potential S100B source [95]. However in a prospective study of over 200 patients Savola [96] indicated that patients with cerebral trauma had significantly (p value < 0.001) higher S100B levels compared to those with only extracerebral injuries. Their main conclusions were that S100B levels did correlate well with the degree of cerebral injury and that it also had a strong negative predictive power with normal levels virtually excluding neuronal injury.

1.3 Summary and Aims of Clinical Studies

1.3.1 Summary

Transoesophageal echocardiography has demonstrated large transcardiac emboli entering the pulmonary circulation after a range of orthopaedic procedures that involve instrumentation of a long bone intramedullary canal. Transient and asymptomatic pulmonary dysfunction and hypoxaemia are often detectable. In addition these procedures can produce systemic effects with transcranial Doppler ultrasonography emerging as a non-invasive method of monitoring and quantifying the systemic (cerebral) embolic load. This monitoring method has been most commonly used in cardiac surgery and a correlation established between cerebral embolic load and cognitive deficits detectable after surgery.

The cerebral embolic load experienced and its relationship to cognitive function after common orthopaedic procedures that generate fat embolic events is currently unclear. Large systemic embolic loads related to forms of pulmonary arterio-venous shunting have been associated with acute confusion. However there is evidence that these episodes represent only the severe end of a possible spectrum of cognitive compromise related to cerebral fat embolic events. Sensitive and validated neuropsychological tests are available to assess cognitive function but have not previously been applied to orthopaedic patients. In addition surrogate serum markers of neuronal injury such as S100B protein are now available and may help to quantify cerebral injury following trauma and subsequent surgery.

1.3.2 Aims of Clinical Studies

Study 1 (chapter 2) Cerebral Emboli and Cognitive Function after Intramedullary Long Bone Fracture Stabilisation.

1. To assess the frequency and distribution of intraoperative cerebral embolic events during intramedullary nailing of femoral and tibial diaphyseal fractures.

2. To perform a range of sensitive and validated cognitive tests after surgery and compare with age, sex and intelligence matched data to assess whether surgery was associated with clinical cognitive dysfunction.

3. To assay levels of a serum marker of neuronal injury (S100B protein) in order to quantify cerebral injury

4. To establish any correlation between clinical cognitive findings and the cerebral embolic load and serum S100B measurements.

Case report (chapter 3) The Cognitive Effects of Fat Embolus Syndrome after an Isolated Femoral Shaft Fracture

This case report describes an isolated femoral diaphysial fracture, stabilised by intramedullary fixation that developed and recovered from fat embolus syndrome. Comprehensive neuropsychological testing over the subsequent eighteen months revealed significant and persistent cognitive dysfunction.

Study 2 (chapter 4) Cerebral Emboli and Cognitive Function after Elective Lower Limb Arthroplasty

1. To assess the frequency and distribution of intraoperative cerebral embolic events during elective cemented hip and knee arthroplasty.

2. To perform a range of sensitive and validated cognitive tests before and following surgery to assess whether surgery produced any clinical cognitive deficit.

3. To assay serum S100B protein levels to quantify better any cerebral (neuronal) injury

4. To establish any correlation between clinical cognitive findings and the cerebral embolic load and serum S100B measurements.

1.4 Damage Control Orthopaedic Surgery

1.4.1 Principles

Injury is a leading cause of morbidity and premature death in the young [97]. The initial treatment of the seriously injured patient has improved. There have been many advances which include: minimising the time at the accident scene; more structured training for those involved with trauma management (e.g. formal Advanced Trauma Life Support (ATLS) for junior medical staff); designated trauma centres have been designed with appropriate and adequate support from allied specialities. The early initiation of resuscitation protocols with early emergency surgery to maintain airway, breathing and control haemorrhage and have been also been attributed to improved patient survival rates after serious injury.

It is now recognised that trauma results in an immediate systemic stress response related to the degree of initial injury [46]. The clinical outcome is determined by the magnitude of the initial insult and by an individual's systemic response both to the initial injury and subsequent treatment. The term 'second hit' has been applied to the process whereby an injured and physiologically vulnerable patient is exposed to further trauma as a result of the surgical management of his injuries [98].

Peripheral limb injuries involving femoral and tibial diaphyseal fractures constitute a leading cause of hospitalisation related to non-fatal injury. The initial treatment of these injuries was often delayed in order to 'optimise' a patient's condition. There were concerns that immediate surgical treatment to stabilise these injuries may worsen prognosis owing to further tissue damage, haemorrhage and fat embolus release. However it was to become apparent that early skeletal stabilisation did in fact reduce the

incidence injury related complications and improve outcome. Riska [99] advocated a policy of early rigid internal fixation in 47 consecutive patients requiring intensive care treatment because of multiple injuries that included at least two long bone fractures. Although there was no control group for comparison the mortality rate and speed of patient ambulation after injury in this study was much improved [99].

Bone [100] et al showed similar reductions in mortality in seriously injured patients with long bone fractures in two separate studies. The first was a prospective study involving patients with acute femoral fractures. A delay of more than 48 hours before intramedullary fracture stabilisation resulted in an increased incidence of respiratory complications in those patients who had significant associated injuries [100]. A subsequent multi-centre trial [101] that involved over 600 patients demonstrated that early (<24 hours) intramedullary femoral fracture stabilisation was responsible for marked reductions in mortality in patients with severe musculoskeletal injuries. By the early stabilisation of peripheral limb fractures, patient mobilisation was encouraged and the length of time spent in both intensive care and hospital subsequently fell. The morbidity associated with prolonged immobilisation was reduced and a fall in healthcare costs clearly demonstrated [66].

A policy of early long bone fracture stabilisation was to be recommended in order to improve patient survival and reduce the frequency of subsequent respiratory and systemic complications [49,66,100]. These complications were attributed to continued haemorrhagic, embolic, coagulative and inflammatory processes, which were thought to become exhaggerated in patients with long bone fractures that were not quickly and adequately stabilised. Improved surgical techniques that involved reamed intramedullary

long bone fracture fixation minimised rates of fracture mal- and non-union whilst permitting early patient ambulation, with no increase in fracture complication rates such as infection or compartment syndrome [100,102]. The term "early total care" was applied to the definitive and early (<24 hours from injury) reamed intramedullary fixation of long bone fractures and was considered the optimal form of treatment and a surgical priority in the seriously injured[66].

However, concerns were raised regarding secondary pulmonary and systemic fat embolic events thought to be linked to reamed intramedullary techniques in the seriously injured [103]. In this review of over a thousand patients with acute femoral fractures a high and unexpected rate of pulmonary complications occurred in young patients with isolated femoral injuries treated by reamed intramedullary stabilisation. Reynolds [104] retrospectively reviewed 424 patients who had acute femoral fractures treated by reamed intramedullary stabilisation. Patients with a low severity of injury benefitted from early stabilisation with fewer respiratory complications. However, this benefit was not seen in patients with a higher injury severity score (ISS>18). It was concluded that modest delays in definitive fracture stabilisation in the more seriously injured cohort did not adversely affect prognosis.

Therefore some concerns were raised over the physiological effects of early reamed intramedullary stabilisation by some trauma centres. These concerns have been investigated extensively by the Hanover group [105-111]. In the early 1990's a retrospective study investigated an apparently high incidence of respiratory complications in patients who had primary reamed intramedullary femoral fixation with an associated blunt chest injury. At that time the Hannover unit was following the policy of 'early total care'. This

review revealed a higher rate of acute respiratory distress in those patients who had a thoracic injury and early reamed intramedullary stabilisation compared to patients who had an isolated chest injury [106]. Their concerns were focused on patients with both a femoral fracture and thoracic injury. The additional pulmonary stresses caused by reamed intramedullary stabilisation may have increased the frequency of acute respiratory distress in this patient sub-group. A subsequent prospective study compared the effects of reamed versus unreamed intramedullary femoral nailing on pulmonary function using invasive monitoring. A transient rise in pulmonary arterial pressure and deterioration in the arterial oxygen concentration (Pa O2) / inspired oxygen concentration (Fi O2) ratio was demonstrated only in the reamed group [112].

A subsequent change in the management of acute femoral fractures in the most seriously injured patients from definitive intramedullary stabilisation to initial external fixation was implemented in this major trauma centre. A retrospective review indicated that this change in surgical protocol was at least partially responsible for improvements in the rates of multiple organ failure and acute respiratory distress subsequently seen [110].

Conservative surgical techniques with reduced operative time and tissue insult had been proposed in seriously injured patients to minimise the 'second hit' caused by surgery and possibly improve outcome. The term 'Damage Control' was applied to these surgical techniques. This term was first used by the United States navy and was applied to a stricken ship where the main objective was to keep the vessel afloat and avoid further damage to the ship's structure. The type of patients thought to benefit from 'damage control' surgical techniques were those who had sustained serious penetrating or blunt injury with persistent hypothermia, coagulopathy and acidaemia

despite resuscitation. In these patients the risk of metabolic failure from surgery was considered greater than the risk of failing to complete the initial definitive procedure [113]. The exanguinating patient with major visceral and vascular damage showed improved rates of survival using abdominal packing (damage control) compared to initial definitive laparotomy [113]. The broad principles of 'damage control' surgery involved:

1. Limited procedures to control haemorrhage and stabilise life-threatening injuries.
2. Physiological patient monitoring within an intensive care environment.
3. Definitive surgery once the patient's condition has been optimised

The anatomical areas where damage control surgery could be applied have become expanded and now include trauma patients with pelvic and peripheral limb injuries [114]. These alternative surgical strategies involve the use of temporary external femoral facture fixation as a 'damage control technique' in order to minimise the 'second hit' of surgery in seriously injured and physiologically vulnerable patients. Delayed conversion to definitive reamed intramedullary fixation is performed once the patient's condition has been optimised.

The use of external fixation is more common after pelvic fractures to reduce pelvic volume and limit blood loss [115]. However, external fixation has also been shown to be a viable alternative to intramedullary stabilisation of femoral fractures and other types of peripheral limb injury in terms of blood loss, intraoperative complications and mortality. Scalea [116] demonstrated that external fixation can provide adequate temporary stabilisation in severely injured patients with a rapid operating time, reduced blood loss and reduced pulmonary embolic load being the potential benefits. This retrospective

review examined the type of patient managed with primary external femoral fracture fixation compared to intramedullary stabilisation. The external fixation group had a higher average severity of injury, a lower Glasgow Coma Scale score on admission and required higher rates of blood and fluid transfusion. Successful delayed conversion to definitive intramedullary fixation was demonstrated and could be performed at an average of 4.8 days following initial treatment. This study demonstrated the use of external fixation as a quick and effective method of achieving long bone stabilisation. However a direct comparison with intramedullary fixation could not be made owing to differences in injury severity between patient cohorts.

Nowotarski [117] demonstrated successful delayed conversion of external fixation to intramedullary stabilisation of femoral diaphysial fractures in the multiply injured. This retrospective review of 1500 femoral fractures admitted to a single trauma unit over a five-year period demonstrated that primary external fixation was used in 4% of admissions. This procedure was again reserved for the more seriously injured patients with a mean Injury Severity Score of 29. This often included associated injuries to the head, chest and abdomen. Conversion to intramedullary fixation was performed at an average of seven days after initial surgery with low infection rates (1.7%).

Advocates of this surgical strategy indicated that following injury, the degree of initial trauma and the patient's subsequent biological response could not be altered. It was hoped that by using initial external fixation, outcome could be improved by reducing the 'second hit' of surgery. Orthopaedic 'Damage Control' enthusiasts emphasised that an accurate assessment of a patient's condition was necessary with the

use of haemodynamic, embolic, inflammatory and coagulative markers to best deciede upon the optimal surgical treatment pathway.

Advocates of 'early total care' argued that the degree of initial injury alone was the sole contributing factor to the development of subsequent systemic complications and that the method of fracture fixation was inconsequential given a background of severe injury [118,119]. Adequately resuscitated patients should undergo immediate and definitive intramedullary fixation.

Although there is much debate about the optimal method of initial fracture fixation in the seriously injured with the arguments falling into two distinct camps there is general agreement about certain issues. First, initial skeletal stabilisation should not be delayed. Second, the degree of initial trauma has a more direct correlation with the development of subsequent systemic complications than the method or timing of any peripheral extremity fracture stabilisation[46]. The main debate has centred upon quantifying the relative physiological effects of fracture treatment compared to the consequences of injury alone. One of the main difficulties is that the incidence of systemic complications after injury such as fulminant ARDS and FES is relatively low [19]. Achieving statistical power and demonstrating a significant difference between two surgical treatment strategies in a prospective fashion is difficult and will require large numbers of trauma patients.

1.4.2 Pathophysiology

In deciding upon the optimal management of long bone fractures in seriously injured patients a number of physiological processes should be considered. These include hypovolaemia, electrolyte imbalance, embolism, inflammation and

coagulopathy [1,46]. The pathophysiology is not fully understood and can be affected by associated injuries (for example to the chest). In addition the timing of the above processes tends to overlap and they operate in synergy to produce tissue hypoxia and end organ damage. A patient's individual response to injury can also vary considerably with acute respiratory distress and major organ dysfunction being the most serious sequelae.

Hypovolaemia An isolated adult femoral shaft fracture can result in a blood loss ranging from 300-1300 ml, with a transfusion rate of 40% (mean 2.5 units packed red blood cells) which is related to the preoperative degree of haemorrhage [120]. In addition blood loss and transfusion requirements have been shown to be higher after multiple lower extremity fractures. A prolonged hospital stay and increased frequency of acute respiratory distress have also been demonstrated[121]. This reflects the increased severity of these injuries which can go unrecognised using conventional injury severity scoring systems [121].

Hypovolaemia that follows injury can directly reduce tissue perfusion and result in inadequate oxygen delivery. Inadequate aerobic metabolism results in subsequent tissue and end organ damage. However, the situation is more complicated than simple haemorrhage. Indirect effects include platelet activation and the production of a hypercoagulable state. The term 'sludge filter" has been applied to the impaired pulmonary and cerebral circulations which occur during such periods of hypovolaemia. [45]

Pro-inflammatory cytokine upregulation during the early phase after injury with associated hypovoaemic shock is also well recognised. The overproduction and expression of cytokines in the early phase after haemorrhagic shock are directly related to rates of acute respiratory distress, multiple organ failure and mortality [122]. Interleukin-6 (IL-6) is an example of an inflammatory cytokine, which can become elevated. This has been shown in haemorrhagic animal models [123] and also in clinical studies where the levels correlate with mortality rate [122]. IL-6 is a predominantly pro-inflammatory cytokine secreted by macrophages and T lymphocytes. It plays an important part in the hepatic acute phase response, which follows trauma. The concentration of IL-6 closely correlates to the degree of hypovolaemic shock and extent of tissue injury. This cytokine also has a relatively long half-life with a peak concentration that occurs 4-6 hours after injury and persists for several days. This makes it a potentially useful prognostic marker after injury. Other pro-inflammatory cytokines such as Tumour Necrosis Factor α and Interleukin-1 both have a shorter half-life and are less useful for detection. However, elevated levels have been demonstrated with animal models of haemorrhage emphasising their important role in the pathophysiology of this process [124]. In addition their role with the breakdown of muscle proteins, may contribute towards further tissue damage which follows hypovolaemic shock [125]. Cytokines represent acute-phase proteins and are implicated in the activation of the complement cascade, C - reactive protein production and the expression of fibrinogen.

There have been studies performed which clearly demonstrate dysfunction at a cellular level after haemorrhagic shock. An alteration of active membrane transport systems (Na+-K+-ATPase pump) can depolarise the cell and result in a loss of cell

membrane integrity [126]. Fluid sequestration into the intracellular compartment can be a major site of fluid loss and adequate resuscitation that involves both blood and crystalloid fluids is necessary to compensate for this process.

Aggressive fluid therapy has the potential to exacerbate lung interstitial oedema. Therefore, the concept of delayed fluid therapy may form part of a 'Damage Control' surgical protocol to avoid this complication in seriously injured patients. There is evidence of improved survival with a delay in aggressive fluid management in hypotensive patients with penetrating injuries [127]. The most recent debates with regard to fluid and haemodynamic management have centred upon minimising lung interstitial oedema by avoiding over-resuscitation. A more prudent and less aggressive administration of crystalloid fluid, with the minimal use of colloid and the prescription of diuretics in severe cases have been proposed as methods of improving respiratory insufficiency following injury. Invasive monitoring of central venous and pulmonary arterial pressures allows a more accurate assessment of hypoxaemia and true haemodynamic status to assess the efficacy of therapeutic intervention.

Metabolic Acidosis and Base Deficit The correction of hypovolaemic shock is paramount to any trauma resuscitation protocol. However, standard measurements of heart rate and blood pressure do not always accurately indicate adequate tissue and end-organ perfusion. 'Oxygen debt' is the deficit in oxygenation that can occur with hypovolaemia and correlates well with reduced end organ tissue perfusion and mortality rates [128]. 'Occult hypoperfusion' is the term applied to a heamodynmically stable patient with persistently elevated lactate levels. This type of patient is inadequately resuscitated

in terms of metabolic acidosis. Crowl [129] demonstrated in patients undergoing early (< 24 hours) femoral fracture fixation, that a two-fold increase in post-operative complications occurred with an elevated lactate level of more than 2.5 $mmoll^{-1}$ prior to surgery. These complications involved a range of systems including cardiac, respiratory (ARDS), neurological and gastrointestinal as well as an increased incidence of infection. It was concluded that patients with occult hypoperfusion are more susceptible to the 'second hit' phenomenon caused by surgery. Adequate heamodynamic and acid-base resuscitation should be achieved prior to surgery in order to optimise outcome.

Blow et al [130] demonstrated higher rates of multiple organ failure and respiratory complications after major trauma in patients with persistent (>24 hours) and uncorrectable occult hypoperfusion with lactate levels that remained above 2.5 $mmoll^{-1}$. The correction of metabolic acidosis (base deficit) appeared to be essential in improving mortality after serious injury. In a prospective study of seriously injured patients Abramson [131] demonstrated a 100% survival in patients whose blood lactate concentration were below 2 $mmoll^{-1}$ by 24 hours after injury. However, only a minority (3 from 22) survived if lactate levels remained elevated at 48 hours. The time taken to reduce lactate levels to a normal level was related to patient survival. Previous animal work has shown the serum base deficit level (i.e. negative base excess) measured by arterial blood gas analysis to be a more accurate indicator of oxygen debt compared with direct measurements of central venous and arterial pressures [132].

Pulmonary Embolism Work performed by Sevitt [10] indicated that hypoxaemia is an important and common problem following long bone fractures owing to pulmonary

fat embolism. This was frequently detectable at a subclinical level with arterial oxygen concentrations which dropped below normal to 60-70 mmHg, but with no corresponding carbon dioxide retention [10]. In this study of 50 patients with isolated long bone fractures, the incidence of arterial hypoxaemia on admission was 64%. Hypoxaemia seemed to relate to the location of the fracture and severity of injury with an 80% occurence with femoral and tibial diaphysial fractures and a 100% incidence after road traffic accidents. Sevitt [10] indicated that the severity of hypoxaemia was directly related to the probable fat embolic load, with higher volumes in severe or multiple fractures. The majority of cases occurred without clinical evidence of hypovolaemic shock and before general anaesthesia was administered. This excluded these other possible causes of hypoxaemia. The primary hypoxaemic events after injury were transient, typically lasting a few days before returning to normal. However in this series, second and third episodes of hypoxaemia occurred after the first and were directly related to operative fixation (plate or nail) and manipulative procedures on the fractured extremity. These episodes were thought to be secondary to new pulmonary fat embolic events related to disturbances at the fracture site. In addition 4 of the 50 (8%) patients were diagnosed as having clinical and systemic features of 'fat embolism' with respiratory distress, cerebral symptoms and petechial skin rash. It was noted that two of these cases had early fracture stabilisation surgery and suggested that serial arterial oxygen concentrations in trauma patients may play a key role in helping to predict the optimal timing for subsequent surgery.

After long bone fracture there appeared to be a measurable pulmonary embolic load and corresponding fall in arterial oxygen concentration. Oxygen therapy improved hypoxaemia during these episodes but never directly proportional to the inspired oxygen

concentrations. A form of right-to-left pulmonary arterial shunting of blood flow to the venous circulation by-passing the pulmonary microvasculature was the likely explanation with a combination of possible causes including: a large embolic load, limited lung filtration capacity, pulmonary vasoconstriction, rise in pulmonary arterial pressure; hypoxia and pre-existing pulmonary disease [21]. By inducing hypoxaemia and pulmonary shunting, the degree of systemic embolisation will increase. Oxygen therapy can help reduce this effect and improve the clinical features such as confusion associated with systemic fat embolisation.

Similar work indicated that the effects of fat emboli were prevalent but often sub clinical. Riseborough [23] confirmed the presence of hypoxaemia in 50% of patients with isolated lower limb fractures. A corresponding decrease in the haematocrit and platelet counts was noted with an increase in fibrinogen degradation products that indicated increased fibrinolysis. An increase in serum lipase was also noted and although there was only a minor increase in the serum triglyceride levels the serum levels of free fatty acids rose sharply.

Therefore after trauma the direct mechanical effects of fat emboli blocking the pulmonary microcirculation can be exacerbated by increased platelet adhesiveness and a stimulation of the fibrinolytic system [133]. In addition the chemical effects of lipase activity which produce toxic free fatty acids can cause direct damage to the pulmonary parenchyma [134]. Increased pulmonary arterial to venous shunting can result producing an increased arterial to alveolar oxygen gradient [23].

Intramedullary pressure changes produced by long bone instrumentation have been correlated with embolus production. Wozasek[135] reamed and nailed intact femurs

and tibias in sheep whilst measuring the intramedullary pressure using a pressure transducer. A marked increase in intramedullary pressure was demonstrated with levels ranging from 300-1400 mmHg and with detection of corresponding transcardiac emboli by echocardiography.

Coagulation The presence of fat and marrow emboli in the systemic circulation after long bone fractures activates the coagulation and fibrinolytic pathways. Surgery further stimulates this thrombogenic process [46,108,136,137]. Pape used a large animal (ovine) model involving haemorrhagic shock, lung contusion and reamed intramedullary nailing of osteotomised bone to demonstrate a consumptive coagulopathy with a reduction in levels of fibrinogen and antithrombin III [108]. A subsequent clinical study performed by the same group quantified changes in coagulation and fibrinolytic parameters in patients following blunt trauma and lower limb fracture [109]. They demonstrated increased perioperative levels of prothrombin fragments 1&2 and fibrin degradation products in isolated femoral fractures, which underwent intramedullary fixation.

This activation and possible loss of coagulation control has been linked to the development of acute lung injury and other systemic complications after major trauma. Intramedullary fixation stimulates the coagulation mechanism and may contribute towards complications seen. Robinson at al studied the correlation between coagulative responses and embolic load [138]. Reamed nailing was seen to activate the coagulative systems with a prolonged activated partial thromboplastin and pro-thrombin times as well as a consumption of fibrinogen and platelets with elevated levels of D-dimer and

thrombin degradation products. The embolic load was found to closely correlate to the degree of activation. A larger embolic load was associated with pathological fractures and a more pronounced coagulative response, with greater hypoxemia, raised pulmonary arterial pressure and respiratory compromise following surgery [138].

Studies have supported the concept of a combined synergistic embolic and coagulative response to produce significant acute lung injury following major trauma. Preactivation of the coagulative system after injury may predispose the patient to an inappropriate and severe response to intramedullary procedures and the thromboplastic emboli released as a result. The more severe clinical responses are associated with a clinical picture similar to disseminated intravascular coagulation [138]. Localised disseminated intravascular coagulation within the lung has been attributed to acute lung injury with the production of microthrombi. In addition a systemic procoagulative state may help explain the systemic features of embolisation without a source for systemic access such as a patent foramen ovale [34].

Inflammation In the minutes that follow a traumatic event, the direct tissue damage and change in haemostasis that can occur, produces an inflammatory response, which develops with time. This involves the activation of monocytes and granulocytes that produce pro and anti-inflammatory mediators [139-141]. These changes can occur locally at the site of injury but are also detected systemically. The term Systemic Inflammatory Response Syndrome (SIRS) has been applied to the generalised inflammatory response that occurs after injury. This initial pro-inflammatory stress response is produced predominantly from macrophages and is primarily involved in

removing damaged tissue and beginning repair processes. Increased endothelial permeability produces an outpouring of exudate into the interstitial fluid space from the capillary beds of damaged tissue and end organs involved to produce interstitial oedema. This initial stress response is relatively short lived and monocytes soon become deactivated being unable to respond to fresh stimuli [142]. In addition a Compensatory Anti-inflammatory Response (CARS) is activated with mediators directly linked to the development of immunosuppression following trauma [46]. Therefore an immune imbalance can result with the patient having a period of increased immune susceptibility. A more pronounced immunodepression is seen with increasing levels of injury with haemorrhage and tissue damage acting in synergy [142]. The effects of this immune imbalance can be to exacerbate shock, increase transudation into end organs, exacerbate coagulation defects and predispose to future infection [143]. This all occurs in the early days after injury and corresponds to the scheduling time for many surgical procedures, which involve further tissue trauma.

A recent development has been the use of pro- and anti-inflammatory markers in the prediction of patient outcome after serious injury. Both may play a role in the determination of which patients may benefit from damage control surgical techniques. In a prospective study of 31 patients involved in a blunt injury, serum IL-6 levels were elevated on admission and decreased gradually with time [140]. As previously stated Roumen [122] demonstrated a correlation between serum IL-6 levels and the development of multiple organ failure and acute respiratory distress in 28 patients following multiple injury. Therefore after blunt trauma, the size of the inflammatory response is related to the initial degree of injury.

Excessive production and release of proinflammatory cytokines can act as specific and sensitive markers for injury severity and aid subsequent management. In a prospective study, Pape [109] demonstrated a comparable increase in IL-6 levels in patients undergoing elective hip arthroplasty with those having intramedullary fixation of an isolated femoral diaphysial fracture. This study also included polytrauma patients and a 'control' group undergoing ankle fixation. The latter group showed no increase in IL-6 postoperative levels whereas the polytrauma group showed the highest pre-operative IL-6 levels with substantial further increases after intramedullary femoral fracture fixation. The effects of intramedullary fracture fixation surgery have been clearly shown not to be inconsequential after major injury.

A subsequent study performed by the same group then demonstrated the potential benefits of 'damage control techniques' the reduction of the acute inflammatory response caused by fracture stabilisation. An increase in pro-inflammatory cytokine measurements (IL-6 and IL-8) was demonstrated in injured but clinically stable patients immediately after early (days 2-4) primary intramedullary femoral nailing. These increases were not detected in patients who underwent initial temporary external fixation with delayed conversion to definitive intramedullary stabilisation 5-8 days later [111]. The patients appeared to demonstrate differing patterns of inflammatory response influenced by the type and timing of fracture fixation. However no overall difference in clinical outcome was demonstrated between treatment groups. It could be postulated that in the seriously injured, such subtle differences in physiological response are important in optimising patient care and reducing the risk of reaching inflammatory thresholds, which could result in pulmonary and other end-organ damage.

Excessive release of pro-inflammatory cytokines appears to be central in the pathogenesis of complications such as acute respiratory distress. During the early phase after injury it has been suggested that the cytokine pro-inflammatory cascade is significantly up regulated within the pulmonary parenchyma to produce a different pattern in concentrations of pulmonary and systemic inflammatory mediators. Keel studied 16 patients with a severe injury (average Injury Severity Score = 34) [144]. Amplified levels of pro-inflammatory cytokines IL-1β and IL-8 were demonstrated from bronchoalveolar lavage samples. However there was no corresponding rise in systemic (serum) concentrations. Measurements of pro-inflammatory cytokines within the lung, but not in the systemic circulation may indicate an amplified local inflammatory response early after injury. This may account for the apparent susceptibility of the pulmonary parenchyma to inflammatory damage after trauma.

The accumulation of neutrophils at inflammatory sites results in excessive release of toxic metabolites and causes tissue injury. The accumulation of neutrophils and proinflammatory mediators has been demonstrated in the alveolar space during early acute respiratory distress along with a corresponding rise in neutrophil enzymes, endotoxin binding proteins and matrix metalloproteinases [145]. These changes indicate that the alveolar space can be converted to an area of intense localised inflammation with the integrity of the alveolar capillary membrane being compromised by proteolytic mechanisms.

Interleukins have been implicated in neutrophil mediated lung injury. The chemo-attractant properties of cytokines in attracting neutrophils into the interstitial space has been previously demonstrated [146]. This prospective clinical study looked at

neutrophils isolated from peripheral blood samples taken from healthy volunteers and from patients after major musculoskeletal trauma. The chemo-attractant properties of IL-8 were demonstrated with enhanced neutrophil migration across porous tissue culture inserts in the injured group. The coupling of enhanced neutrophil migration with elevated IL-8 levels may be central to the development of pulmonary and end-organ inflammation.

Neutrophil activation produces proteolytic enzymes such as elastase, which can produce cell injury and organ dysfunction. Plasma elastase levels are a measurable and sensitive indicator of neutrophil activity which have been correlated to the severity of injury and subsequent multiple organ failure. Nuytinck [147] prospectively analysed elastase levels in 71 trauma patients and found a correlation with injury severity and the development of acute respiratory distress syndrome. This corresponded to subsequent studies which have looked at methods of quantifying trauma from neutrophil elastase levels [140].

Changes occur not only in the circulating white cells, but also in the endothelial lining of the capillaries. Upregulation of adhesion molecules results in the adherence of activated neutrophils facilitating their migration from the circulating blood into the interstitial space where they can cause localised effects [148]. At a cellular level defects in aerobic metabolism occur with reduced ATP production. Anaerobic metabolism occurs and produces excessive lactate which can alter protein production with enzyme and cell dysfunction resulting in cell death [149].

In summary immunological evaluation may offer an accurate method to categorise patients and quantify the degree of initial injury in order to determine the

optimal surgical strategy. In addition it could help identify at an early stage which patients are developing acute respiratory and systemic complications unexpectedly after less severe and isolated injuries.

Associated Injuries Many clinical risk factors have been identified as influencing patient outcome after trauma. These risk factors can be broadly split into direct and indirect categories.

Direct factors that are associated with local pulmonary parenchymal injury include: aspiration, pneumonia, pulmonary contusion and toxic inhalation. Indirect factors include: sepsis, multiple transfusions, over-aggressive fluid management, disseminated intravascular coagulation and multiple fractures.

Severe chest injury is the most relevant to orthopaedic trauma patients where there is debate regarding the optimal method of fracture fixation in order to avoid further pulmonary damage secondary to pulmonary embolus, coagulation and inflammation. As previously stated, a higher Injury Severity Score increases the likelihood of developing respiratory and systemic complications after injury. Ertel et al demonstrated this point in a retrospective review of 1278 trauma patients [150]. A correlation was established between: injury severity score (ISS); the systemic inflammatory response to trauma (SIRS) and and the incidence of acute respiratory distress and multiple organ dysfunction.

1.4.3 Previous Animal Research in this Field

Animal research in this area has centred on the effects of fracture stabilisation, in a variety of canine, porcine and ovine models [105,151-154].

Schemitsch examined pulmonary fat embolic events in a canine model of long bone (femur and tibia) pressurisation and subsequent surgical osteotomy [41]. The effects of the timing and type of long bone stabilisation were examined. Firstly, pulmonary fat embolic events were created by reaming and cementation (with pressurisation) of intact bone. An osteotomy was then performed through the bone diaphysis. Animals were divided into two main groups with fracture fixation at four and at twenty-four hours after embolic showering. The two groups were then subdivided depending on the type of fixation technique. The fixation techniques used were plating, nailing without reaming and nailing with reaming. Outcome measurements included pulmonary arterial pressure, alveolar-arterial oxygen gradient and post-mortem examination of end organs (lungs, brain and kidney) for intravascular fat. There was no difference between subgroups with regards to intravascular fat embolism and pulmonary arterial pressure at either time point. In both intramedullary fixation groups substantial (3-4 times) increases in alveolar-arterial oxygen gradient were seen if the fixation was performed at four hours compared to no change with plating. This would indicate a marked temporary increase in the degree of pulmonary arterial-venous shunting. Despite these findings the authors concluded that the method of fracture fixation had no effect on the development of pulmonary dysfunction.

Neudeck and Wozasek studied intramedullary pressure, fat embolisation and pulmonary responses in adult sheep after blunt chest injury [154]. Reamed nailing after surgical osteotomy was compared to the effects of plating. Nailing produced the most intense embolic showers on echocardiography but no significant difference in pulmonary arterial pressure was seen between groups after surgery. It should be noted

that the physiological effects of chest injury alone were substantial with a 60% fall in systolic arterial blood pressure and a corresponding rise in pulmonary arterial pressure from an average of 20 to 44 mmHg after injury (which would indicate marked hypoxaemia). This recovered quickly with resuscitation prior to fracture fixation and minimal subsequent rises in pulmonary arterial pressure were seen to follow both nailing and plating fracture fixation.

Pape compared the effects of reamed versus unreamed femoral nailing in an ovine model of hypovolaemic shock and lung injury [105]. Lung contusion was created by manually squeezing the middle and lower lung lobes after preparation of a lung lymph fistula. Incremental bleeding then induced haemorrhagic shock. Each animal was resuscitated over a period of 48 hours and a comparison made between the effects of reamed and unreamed nailing of an intact femur. Both groups were found to have an increase in lung capillary permeability. However acute increases in pulmonary arterial pressure and pulmonary triglyceride levels were only observed in the reamed group. Pape indicated that this had clinical relevance with regard to the development of less invasive fracture fixation strategies in hypovolaemic patients who have an associated chest injury.

However, the relevant findings of the above large animal models may be compromised by the circumvention of crucial steps in injury pathophysiology. The effect of intramedullary instrumentation of an intact long bone or surgically osteotomised bone is likely to be different from that observed in the presence of a fracture which permits a venting effect on pressurised intramedullary contents. Wozasek

eluded to this fact by measuring marked differences in intramedullary pressure generated on intramedullary stabilisation procedures performed upon intact and osteotomised femurs [154,155]. In addition, the pathophysiology of an uninjured, stable model or one, which has been artificially bled to create hypovolaemia, is likely to be different from that existing after true traumatic injury. In Pape's haemorrhagic model, each animal was resuscitated and allowed a complete recovery over a 48-hour period prior to femoral reaming and nail insertion into intact bone. The soft tissue component of these injuries is therefore avoided along with the associated haemorrhage and inflammation from damaged skin, fat and muscle, which surrounds a high velocity long bone fracture.

The Edinburgh Orthopaedic Trauma Unit has recently designed a large animal (ovine) model of major trauma to better mimic the true clinical situation. Using terminal anaesthesia a mechanical pneumatic actuator (ram) was used to create high energy comminuted femoral and tibial fractures of a consistent and reproducible configuration. An initial study primarily examined the immediate physiological effects of this trauama. The work formed part of an MD thesis entitled 'The Pulmonary and Systemic Response to Trauma' published in 2005 by Mr T.O. White (Specialist Registrar, Orthopaedics and Trauma, Edinburgh Royal Infirmary). A substantial haemodynamic, embolic and coagulative response was demonstrated following femoral and tibial fractures. Specifically, an immediate depressant response on the cardiovascular system occurred after injury with a fall in blood pressure and heart rate. This effect is unusual in that one would expect a 'sympathetic' response to follow injury and produce a tachycardia. The

explanation given by Mr White was that sheep are a preyed species and as such can exhibit a marked parasympathetic response to nociceptive stimuli. This phenomenon has been termed the 'Bezold-Jarisch' reflex [156]. Bradycardia, bradypnoea and hypotension occur as a result and the animal 'withdraws' in an attempt to protect itself from further attention and subsequent injury.

The transoesophageal echocardiography techniques that had been used in previous studies by the same unit were also used in this large animal trauma model. Pronounced pulmonary embolic material was seen after each femoral fracture, with smaller amounts detected after tibial fracture and intramedullary fracture fixation.

The initial findings of this study formed the basis for the following proposed work on the effects of different femoral fixation techniques after severe blunt injury and associated hypovolaemia.

1.5 Summary and Aims of Animal Study

1.5.1 Summary

The pathophysiological events, which follow major trauma involving femoral fractures and subsequent treatment, are not fully understood but have implications for patient morbidity and mortality. There is currently substantial controversy regarding the optimal method of treating patients with divergent views. A problem with much of the published clinical work is a lack of standardisation. Analysis from different trauma centres with different resuscitation and treatment protocols is often retrospective over a number of years when factors other than the type of fracture fixation will have changed and possibly improved. For example, the published clinical review from Hanover [106]

compares patients who were treated by early total care and those by damage control techniques, but over two separate time scales. Factors such as improved initial emergency and intensive care therapy may have contributed to the improvements seen in patient outcome. The previous animal research in this area has aimed to standardise the level of injury, timing and method of treatment in order to examine the physiological processes involved in a more controlled and sequential manner. However the conclusions reached may be partially invalidated by weaknesses in some of the models used.

Clinical studies performed by the Hanover and Leeds groups would indicate that there is biochemical support for damage control surgery with levels of inflammatory markers such as IL-6 being influenced by the method of fracture stabilisation. However, the clinical relevance of this in a background of severe injury has been debated.

The Edinburgh Trauma Unit in has been involved in studying the embolic, coagulative and inflammatory responses to long bone fractures and their subsequent stabilisation[1,138,157-160]. Initial interest was in the embolic events, which follow intramedullary procedures such as reaming and nailing in both traumatic and pathological fractures using transoesophageal echocardiograph (TOE) techniques. This was subsequently developed with studies which measured the activation of the coagulation cascade after trauma and surgery and a correlation was established to the transcardiac embolic events visualised on TOE. Recognising some of the inherent limitations of previous published animal and clinical work a large animal model of major trauma was developed to primarily examine the immediate effects of trauma. A previous study using this model confirmed its suitability in creating high-energy reproducible

fractures with an immediate haemodynamic, embolic and coagulative response. This model will allow a comparison to be made of different surgical strategies for long bone fracture fixation.

1.5.2 Aims of Animal Study

Study 3 (chapter 5) Embolic, Coagulative and Inflammatory Responses to Major Trauma and Subsequent Treatment in a Large Animal (Ovine) Model

1. Clarify the sequence of pulmonary and systemic pathophysiological responses over a 24-hour period following bilateral femoral shaft fractures and hypovolaemic shock.

2. Compare the effects of 'damage control' and 'early total care' stabilisation techniques.

3. Measure the intramedullary pressure generated by a high-energy femoral fracture.

1.6 General Overview of Data Presentation and Analysis

The statistical methods of this thesis were used with the SPSS software package version 11.0 (SPSS Inc. Chicago, Illinois). Professional statistical advice was obtained from Dr Catriona Graham of the Wellcome Institute, Western General Hospital, Edinburgh. A result difference was taken to be significant when a p value of 0.05 or less was obtained.

Numerical data points were plotted to determine whether there was a normal distribution. The programme using the Shapiro-Wilk W test tested the scatter of this raw data. This produces a W statistic, which if significant (<0.05) indicates that the distribution of the data is not normal.

To analyse two related numerical data sets a *paired t-test* (parametric) or *Wilcoxin signed rank test* (non parametric) was applied depending on the data distribution. Two unrelated numerical data sets were similarly analysed using either an *unpaired t-test* (parametric) or *Mann Whitney U test* (non parametric). If a number of independent groups were involved and the data normally distributed then a *one-way Anova* calculation was applied and 'p' values for statistical significance identified. *Post hoc Student's t tests* were used to compare two independent samples if a difference was identified. Non-parametrically distributed data over a number of independent samples was analysed using the *Kruskal-Wallis test* as an equivalent to the *one-way Anova*. A *Mann-Whitney U test* was then applied to compare two independent samples.

A correlation analysis was used to determine the degree of association between two numerical variables. This primarily involved a *scatter diagram* of plotted individual

pairs of values. A *Pearson correlation coefficient* was used to establish the sign (direction) and magnitude of correlation.

The specific statistical tests used are described in each chapter. Normally distributed data were presented as a Mean with 95% confidence intervals shown in the parenthesis. Data not normally distributed were presented as the Median with the interquartile range shown in the parenthesis.

Chapter 2 Cerebral Emboli and Cognitive Function Following Long Bone Fractures and Intramedullary Stabilisation

2.1 Introduction

This study aimed to assess the frequency of intraoperative cerebral embolic events during intramedullary nailing of femoral and tibial diaphysial fractures. A range of sensitive cognitive tests were performed and assayed serum S100B protein levels used to assess whether nailing was associated with measurable clinical cognitive dysfunction or cerebral (neuronal) injury and whether these correlated with intra-operative cerebral embolic events.

2.2 Patients and Methods

Lothian Local Research Ethical Committee approval and written consent was obtained. Twenty-seven patients (17 male and 10 female) with a median age of 36 years (inter-quartile range 28-62 years) were recruited. Inclusion criteria were femoral or tibial diaphysial fractures requiring intramedullary stabilisation under general anaesthesia. Exclusion criteria included patients aged under 16 or over 80 years and a past medical history of cerebrovascular disease or cognitive impairment. 12 patients had an isolated femoral shaft fracture (3 pathological), 14 isolated tibial fractures (2 open (grades 1 and 3a respectively[161]) and one patient had 3 closed fractures (femur, tibia and humerus).

Intramedullary (T2 system, Stryker Trauma, Geneva, Switzerland) reamed (Zimmer Intramedullary Reamers, Indiana, USA) fracture stabilisation was performed with the patient in a supine position under general anaesthesia using previously described standard operative techniques [162,163]. On the third day after surgery a short

cognitive screen was implemented involving a range of validated and sensitive cognitive tests. These included: Weschler Test of Adult Reading (WTAR) [86]; Colour Trail Making Tests parts I and II [164]; Controlled Oral Word Association Test (COWAT) [87]; Mini-Mental State Examination (MMSE) [38]; Digit Span and Word List Subtests from the Weschler Memory Scale (WMS-III) [85]. A brief description of each test is given in table 1 with a summary of the test and its application to follow. On initial pilot studies accurate assessment of pre-operative cognitive function proved to be difficult owing to the acute nature of admissions, with opioid analgesic administration and patient anxiety. In addition, the lack of available parallel versions of the tests would have rendered repeat testing over such a short time span subject to a practice effect. Therefore the post-operative cognitive scores were compared with the Predicted Full Scale Intelligence Quotient (PFSIQ) (%) for each patient.

Table 1

Description of Cognitive Tests Applied

Cognitive Tests	Description
WTAR[86]	Predicted Full Scale Intelligence Quotient. (%)
Colour Trails Tests 1&2[84]	Sustained and divided attention, hand-eye motor coordination, sequencing and speed.
COWAT[87]	Verbal fluency
MMSE[38]	Global cognitive function
Weschler Memory Scale (WMS-III)[85]	Digit span: immediate recall (numbers) Word list subtest(s): ■ Word List A – immediate recall ■ Word List D – delayed recall ■ Retention score ■ Interference score

Weschler Test of Adult Reading (WTAR) [86]. This allows an estimate of an individual's pre-morbid intelligence level and can be used to predict cognitive function. It is composed of a reading list of fifty words whose pronunciation gradually increases in difficulty. The patient reads out load the reading list of fifty words from and the examiner has each exact pronunciation on a scoring form. The WTAR is an effective method of indicating a patient's Predicted Full Scale Intelligence Quotient (PFSIQ) (%). It relies on the fact that reading recognition is relatively stable and unaffected by decline caused by brain injury.

Colour Trails Test (CTT) parts 1 & 2 [84]. These two tests involve complex visual scanning with a motor component. The materials required are: Colour Trails 1 Test Sheet (practice trial on one side and test trial on the other); Colour Trails 2 Test Sheet (practice trial on one side and test trial on the other); Stopwatch and lead pencil. Each patient must be able to recognise Arabic numerals (1-25) and distinguish the colours pink from yellow. The pencil was used to connect the circles and sufficient hand-eye coordination must be present to perform this task. A person with no formal training in psychological testing can perform the administration and scoring for each CTT. Instructions for the CTT were given verbally. For the CTT part 1 each patient was instructed to connect the circles numbered 1 through 25 in consecutive order, as rapidly as possible using the lead pancil. A practice trail (numbered 1 through 8) was completed prior to the actual trail test. If an error is made the examiner corrected the respondant and the task was then continued. Ten seconds were allowed for the patient to make a

connection between circles, after which the examiner pointed to the next correct circle before the patient was allowed to continue.

The CTT test 2 again involved the patient rapidly drawing a line between numbered circles in sequence. However, with this trail each number was shown in two separate colours (pink and yellow). The patient connected the numbers in sequence (1 through 25), but alternated between colours (pink 1 to yellow 2 to pink 3). Prior to proceeding with trail 2 the patient completed a practise trail (1 through 8). The examiner recorded the length of time required to complete the test trail.

CTT part 1 provided a measure of sustained attention, perceptual tracking and mental sequencing skills. CTT part 2 is a more difficult task which involved both alternate colour and number sequences. It therefore measured the above cognitive skills and in addition delbt with divided attention and sequencing skills, which involved more than one thought/stimulus simultaneously. These tests are sensitive to the effects of brain injury (especially to the frontal lobe) and help measure cognitive ability and the severity of any impairment [165].

Controlled Oral Word Association Test (COWAT) [166]. The purpose of this test is to measure a patient's ability to produce words of a given letter in a limited amount of time. This test was used as an indicator of neurocognitive ability and reflected verbal association fluency. It is a test often used to compare neurologically impaired individuals with controls and can detect verbal communication deficits following brain injury [87]. The reasons for poor performance can vary. Repetition of the same words indicates an inability to do two things at once (i.e. generate and self monitor). A limited

number of words can reflect poor verbal recall. The method of test administration has been documented [87]. No specific material is required other than a stopwatch. The patient is asked to speak as many words as possible starting with a given letter of the alphabet in one minute. The letters F, A and S were used over three separate one minute tests. Differences in vocabulary size occur for each letter (with F, A, and S, F has the lowest and S the highest) [167]. Patients are instructed to avoid the names of people and places and proper nouns. They are also not allowed to use the same word again with a different ending (e.g. age and aging). The examiner writes down the words spoken by the patient in order. Repitition is assessed by asking if an alternate meaning was intended at the end of each one-minute period (e.g. "son" and "sun"). All three letters are administered and the raw score calculated from the sum of all admissible words. This data is compared with normative adult data corrected for age and level of intelligence to obtain a percentile value.

Mini-Mental State Examination (MMSE) [38] This commonly used test represents a method of detecting gross impairment of specific cognitive skills. Subjects answer questions and complete short tasks being given a score from 0-30 with the range 24-30 indicating that an individual is cognitively intact. It is often used to distinguish patients with Alzheimer's disease from normal elderly individuals [168].

Digit Span and Word List Subtests from the Weschler Memory Scale (WMS-III) The Weschler Memory Scale, third edition (WMS-III) [85] is a well-validated instrument for testing memory function and attention [169,170]. It consists of several subtets, which

cover immediate and delayed memory function. Digit span involves the repetition of a series of numbers read by the examiner to the patient. The length of the number series is gradually increased until the patient can no longer repeat the number series. This test is then repeated using different numbers but this time the patient must repeat the number series in reverse order. The word list subtests involved the immediate recall of twelve words (Word list A) read out by the examiner one at a time with a high score indicating efficient learning. This is repeated four times. A 2nd list (Word list B) is then read out (twelve words) and again the patient asked to verbally recall as many words as possible. An interference score is then obtained by asking the patient to repeat as many words as possible from the original list (Word list A). The interference score assesses memory consolidation and the extent to which the presentation of new material proves to be a distracter. A delayed word recall (Word list D) and retention score is obtained by asking the patient to repeat as many words as possible from Word list A, twenty-five minutes later.

A trained consultant clinical psychologist (Dr Lorna Torrens, Robert Ferguon Unit, Edinburgh Royal Infirmary) reviewed the raw data obtained from each of the above tests. Raw scores were compared to normative data based on the patient's age and intelligence and a percentile value obtained.

The first seven patients underwent cognitive assessment only to establish that the cognitive screen could be successfully implemented. The next 20 patients underwent cognitive testing, with pre- and intraoperative transcranial Doppler ultrasound monitoring for the detection of cerebral embolic signals.

A portable instrument (Companion III, Nicolet Biomedical Inc, Madison, USA) was used with a 2-MHz probe applied percutaneously to locate either the left or right middle cerebral artery, through the transtemporal sonographic window [171]. This window represents an area of relatively thin bone tissue where the ultrasound signal from the middle cerebral artery can be best identified without excessive signal dampening. It is located just above the zygomatic arch and allows direct medial insonation of the middle cerebral artery. The middle cerebral artery is a direct continuation of the internal carotid artery and runs laterally carrying approximately 80% of blood flow to each cerebral hemisphere. The middle cerebral artery is located 30-60 mm deep to the skin surface with a blood flow towards the ultrasound probe. Ultrasound signal depth was altered to obtain the clearest signal with a range between 48-60 mm. A 15-minute reading was taken prior to fracture stabilisation to locate the middle cerebral artery and monitor for embolic events.

Continuous monitoring of the entire intramedullary fracture fixation was undertaken with the procedure being divided into five phases.

1. Pre-operative monitoring, patient positioning and surgical approach.
2. Intramedullary access (bone awl and guide wire insertion)
3. Intramedullary reaming
4. Intramedullary nail insertion
5. Proximal and distal locking screw insertion to wound closure

All recorded embolic signals were then analysed by two experienced technicians (Independent Vascular Services, Wythenshawe Hospital, Manchester). They used established guidelines for emboli detection [172] to remove any artefacts and documented the true number of cerebral embolic signals detected in each patient.

Serum S100B protein levels were measured in the 20 patients who underwent transcranial ultrasound monitoring. A Sangtec 100 ELISA immunosorbent assay (Diasorin Inc. Stillwater, Minnesota, USA) was used. 5 ml of blood were collected from the antecubital vein before surgery and at 0, 24 and 48 hours after surgery. This sample was placed in a 5.5ml serum plastic tube and allowed to clot for 30 minutes at room temperature before being centrifuged at 1000rpm for 10 minutes. Serum was pipetted and stored at -80^{0}C for subsequent batch analysis. The principal investigator performed the analysis. A brief method description follows.

Samples were mixed in a vortex and 50 µl of calibrators, controls and the unknown samples mixed in the ELISA wells. 150 µl of conjugate was placed in each well and the plate was incubated for 2 hours at room temperature on a plate shaker (800rpm). Each well was washed 3 times with 300 µl of wash buffer and 100 µl of Tetramethylbenzidine (TMB) substrate was added. The ELISA plate was then incubated at 800rpm for a further 15 minutes. 10 µl of stop solution was added and the plate read at 450nm. The detection limit is 0.03 $\mu g\ l^{-1}$ with a reference range cut-off established to 0.15 $\mu g\ l^{-1}$ and a measuring range of up to 5 $\mu g\ l^{-1}$.

2.3 Statistical Methods

The cognitive results after surgery were expressed as mean and median percentile differences of each cognitive score (%) compared to the predicted pre-morbid

score (PFSIQ %). Data were analysed as described in Chapter 1.6. A paired t-test or Wilcoxon signed-rank test was used to determine if this difference was significant (p-value of < 0.05). The type of test used depended upon whether the data was normally distributed

A Mann-Whitney U test compared median cognitive test differences and S100B protein levels of those patients who had cerebral embolic events and those who did not. This determined any correlation of both these measurements to cerebral emboli detection *per se*.

Scatter plot graphs with a Spearman's rank correlation coefficient were used to determine the relationship between cognitive test differences and S100B protein levels.

2.4 Results

Cognitive Assessments (n=27). One patient who underwent ultrasound monitoring could not be cognitively assessed since further soft tissue surgery was required. There were no episodes of acute confusion after surgery with a median MMSE of 28 (interquartile range 27-29). The mean/median differences between the predicted pre-morbid PFSIQ (%) and cognitive scores (%) achieved by each patient after fracture stabilisation are summarised in Table 2. Patients scored significantly ($p<0.05$) poorer than predicted on the digit span and with word list A (immediate) and D (delayed) parts of the Weschler Memory Scale (WMS) III. Digit span is a measure of 'working memory' or the ability to hold information and formulate a response. The word list tasks, measure immediate and delayed memory recall of unstructured verbal material. 'Interference' and 'Retention' scores were also poorer than predicted. This would indicate that the patients memory was significantly ($p<0.05$) hindered by the presentation of additional material, similar in content and structure, in between recall trials.

Cerebral Emboli Detection (n=20) Four patients had detectable cerebral embolic events with counts of 2, 3, 3 and 9 respectively. The highest cerebral embolic load occurred after intramedullary fixation of a pathological femoral fracture secondary to a metastatic deposit from small-cell lung neoplasia. The other three patients had isolated tibial fractures (2 closed and 1 open). The distributions of embolic events over the phases of each stabilisation procedure are demonstrated in Graph 1. The majority were detectable during and immediately after procedures, which involved bone and intramedullary instrumentation.

Assessment of Neuronal Injury - S100B Protein Level (n=20) The sequential serum S100B protein levels are demonstrated in Graph 2. The pre-operative median [interquartile range] was 0.20 [0.15 to 0.38] $\mu g\ l^{-1}$, which is above the normal reference range of 0.03 to 0.15 $\mu g\ l^{-1}$. This increased to a peak immediately after surgery (time 2) of 0.51 [0.21-1.18] $\mu g\ l^{-1}$ before falling back to 0.19 [0.15-0.28] $\mu g\ l^{-1}$ by 48 hours post-surgery (time 4). Two patients had markedly elevated pre-operative (time 1) levels of 1.42 and 1.15 $\mu g\ l^{-1}$ respectively. One had sustained a grade 3B open fracture of the tibia, whilst the other had closed multiple long bone fractures (femur, tibia and humerus).

Comparison of Cognitive Function, Cerebral Embolic Load and S100B Protein Levels (n=19) Mann-Whitney U comparisons of cognitive test differences and postoperative S100B protein levels between those patients who had detectable cerebral embolic events and those who did not indicated no significant differences between cohorts.

However, the patient with the highest embolic load (pathological femoral fracture) performed in the bottom 2% of the population in colour trails tests. Her PFSIQ score indicated that she should be within the top 25% of the age-matched population. Therefore this discrepancy using a highly sensitive cognitive measure is indicative of significant difficulties with skills that include sequencing, sustained and divided attention and hand-eye coordination.

Scatter plot graphs with Spearman's rank correlation coefficients indicated only a significant correlation between S100B protein levels and poorer colour trails test 1 performance ($r = -0.614$, $p=0.011$).

Table 2

A. Mean changes in the measured cognitive scores taken 3 days following intramedullary fracture stabilisation compared with the predicted pre-morbid score (PFSIQ %) (95% confidence intervals are shown in parentheses, p values refer to the t-test analysis of the differences between the paired scores, * = $p<0.05$)).

	Mean change (95% C.I.)	P-value
Colour trails 1	-9 (-23 to 5)	0.177
COWAT	-9 (-23 to 4)	0.168
Digit span	-15 (-26 to -4)	0.010 *
Word list A	-30 (-42 to -17)	0.000 *
Word list D	-21 (-33 to -10)	0.001 *
Interference	-21 (-37 to -5)	0.012 *
Retention	-15 (-28 to -1)	0.032 *

B. Median changes in the measured cognitive scores (non-parametric) taken 3 days following intramedullary fracture stabilisation compared with the predicted pre-morbid score (PFSIQ %) (interquartile (IQ) range shown in parentheses, p values refer to the Wilcoxin signed rank test analysis of the differences between the paired scores, * = $p<0.05$)).

	Median change (interquartile range)	P-value
Colour trails 2	5 (-19 to 19)	0.904

Figure 1

Distribution of cerebral emboli during each phase of intramedullary stabilisation

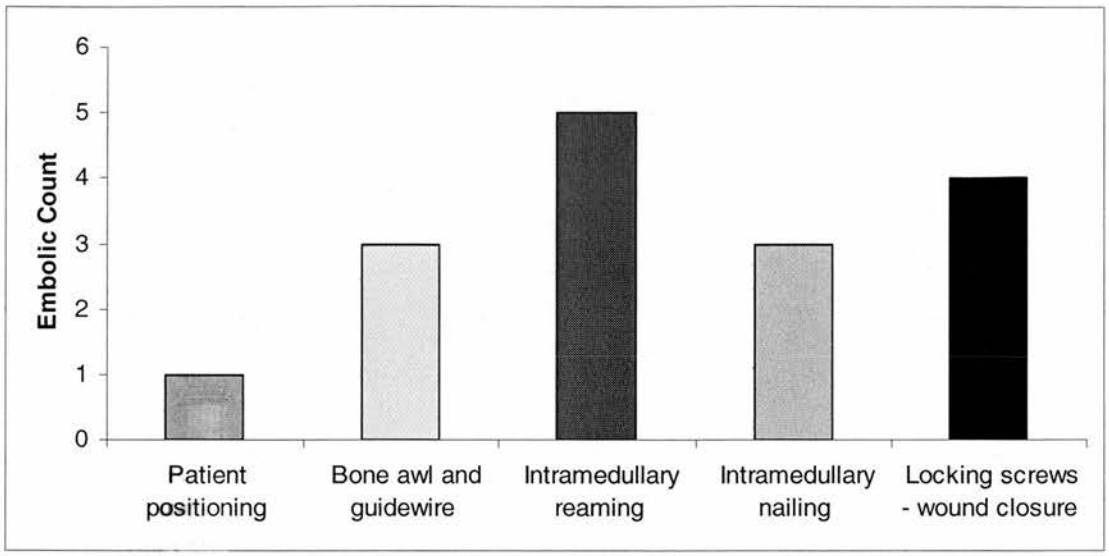
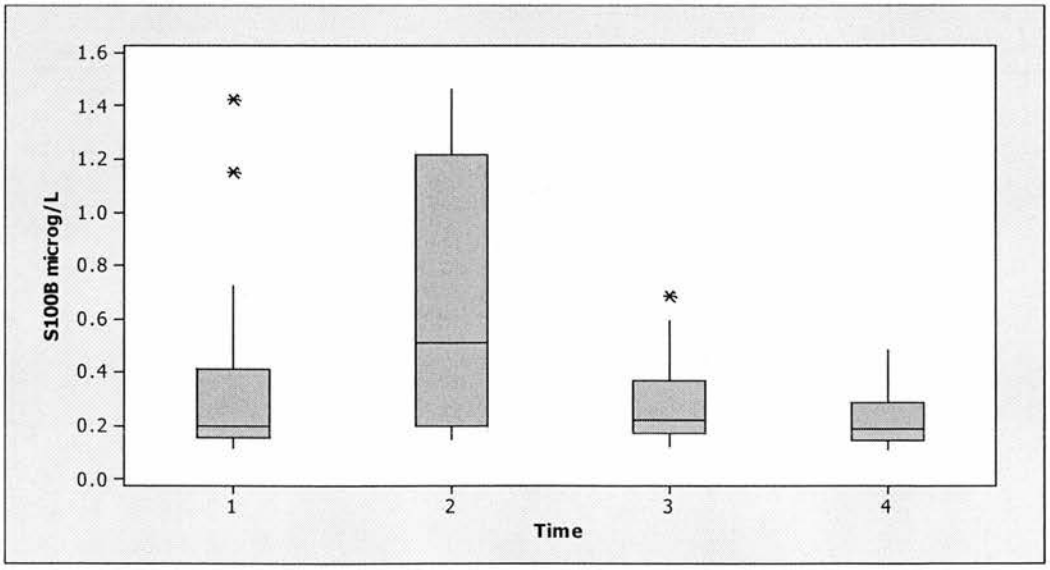


Figure 2

Median serum S100B Protein concentrations pre-operatively and at 0, 24 and 48 hours following intramedullary fracture stabilisation (Interquartile Range shown between error bars. Asterisks represent individual measurements above the Interquartile Range) (reference range 0.03 to 0.15 μg l^{-1}).



2.5 Discussion

The main cognitive findings of this study were specific and quantifiable defects in cognitive function after surgery without any evidence of acute confusion. First, patients performed significantly poorer than predicted on a test, which requires them to repeat number sequences of increasing length (digit span). Secondly, patients performed more poorly than would have been anticipated on a test of verbal recall in both immediate and delayed conditions. Furthermore, interference scores indicated that memory consolidation was adversely affected by the presentation of additional material. Four of the twenty patients monitored had small cerebral embolic loads but with no difference in cognitive testing compared with the other patients. The majority of cerebral embolic events were correlated with instrumentation and reaming of the medullary canal. S-100B protein levels peaked immediately following surgery and a correlation was established with Colour Trails 1 results which is a sensitive and validated test used to detect subtle cognitive impairment following cerebral injury [165].

Why patients should perform significantly more poorly than would have been predicted by this test of verbal memory is not entirely clear. The fact that there was a similarly depressed performance in digit span testing might suggest that the difficulty was attentional rather than a function of memory. Such an observation is supported by the additional finding that memory consolidation of words (i.e. word list A) was adversely affected by the presentation of additional, distracting material. Tests were deliberately selected to be short but sensitive. However, it may be that attention/concentration is limited at this early post-operative stage.

The early cognitive changes after acute intramedullary fracture stabilisation may also relate to the sensitivity of the tests being implemented. Cognitive impairment after cardiopulmonary bypass surgery is well recognised and has a variable incidence of between 20-80%, depending on the sensitivity of cognitive tests used [173,174]. The intra-operative cerebral embolic load has been identified as a main predictor of relative long term cognitive deficit following by-pass surgery [68]. However cerebral embolic loads of 100-200 signals are required before a cognitive decline is detected [173]. The fracture patient cohort in this present study did not experience this size of cerebral embolic load. High (i.e. > 200) numbers of cerebral emboli have produced acute confusion following lower limb arthroplasty with the degree of embolisation directly related to pulmonary arterio-venous shunt size [28]. This may also explain observations of acute confusion related to a patent foramen ovale [40].

Christie et al [1] demonstrated a higher pulmonary embolic load with intramedullary stabilisation of pathological fractures. In our study the highest cerebral (systemic) embolic load was detectable with such a fracture. The distribution of emboli also indicated a higher frequency during intramedullary canal instrumentation that again corresponded to this previous work.

Cerebral embolic events which follow stabilisation of long bone fractures have been previously documented using transcranial Doppler ultrasound [34]. Of the five patients analysed, all had detectable cerebral embolic signals after surgery, but only one had evidence of a right-to-left pulmonary shunt. It has been postulated by Sevitt [21] and confirmed on a large animal model [39] that fat emboli are able to traverse the pulmonary microvasculature and become systemic. This may explain cerebral emboli detection in

the absence of pulmonary venous to arterial shunting. In Forteza's study [34], all five specifically picked cases had clinical evidence of acute confusion after surgery with four which fufilled diagnostic criteria for fat embolus syndrome. This group of patients are therefore not a comparable cohort to this present study. No intraoperative ultrasound monitoring or formal cognitive testing was performed, with emboli counts of up to 70 being detected 1-2 days after intramedullary fracture stabilisation. This relatively large number of embolic events could be explained by the different patient cohort, but also by the lower threshold set for emboli detection at the time [175]. The newer emboli criteria used in our own study [172] required an amplitude of greater than 7dB (compared previously to 3 dB) higher than the background blood flow, thus classifying previously perceived embolic signals as artefacts.

Forteza has also used transcranial Doppler techniques to optimise and protect a trauma patient exhibiting acute confusion and early clinical signs of fat embolisation [176]. A marked reduction in cerebral fat embolisation was demonstrated with percutaneous closure of a patent foramen ovale (PFO) in a young patient after a high velocity isolated femoral fracture. The pre-operative PFO detection and treatment prior to intramedullary femoral stabilisation helped reduce the detectable degree of cerebral embolisation. The patient's neurological status subsequently recovered over the next 36 hours with fracture stabilisation surgery delayed until 10 days after injury when there was no detectable pulmonary to systemic embolisation. It is important to note that even after PFO closure; intramedullary fracture stabilisation produced a second rise in cerebral emboli detection indicating passage through intrapulmonary shunts or incomplete filtering by the pulmonary capillary microvasculature.

Transcranial Doppler ultrasound is therefore a non-invasive monitoring method of predicting which patients are being exposed to a relatively high intra- and postoperative degree of cerebral and systemic embolisation. This may alter the type and timing of initial orthopaedic surgical treatment. In addition transcranial Doppler ultrasound can offer a relatively fast and non-invasive method of identifying pre-operatively, those patients who have a patent foramen ovale or large pulmonary artero-venous shunt (i.e. those most at risk of systemic embolisation). This can be ascertained by performing the 'bubble test'. It involves the intravenous injection (20mls) of a saline and air mixture ('agitated slaine') whilst the patient performs a Valsalva manoeuvre [28]. This test detects pulmonary artero-venous shunting. A correlation has previously been established between shunt size and cerebral embolic load during orthopaedic intramedullary procedures [28].

Postoperative cognitive dysfunction after non-cardiac surgery has been previously documented in the elderly population and is linked to increasing age and duration of anaesthesia [177]. In a large multicenter study of younger patients aged 40-60 years undergoing a variety of surgical procedures, the incidence of postoperative cognitive dysfunction was 19.2% at one week compared to a background level of 4% in age-matched control subjects [178]. This incidence had fallen to 6% in the surgical cohort by 3 months after surgery. The cognitive testing methods used were sensitive and similar to our own study. There was no significant correlation in this younger cohort between postoperative cognitive dysfunction and the duration of anaesthesia. However an unexpected finding was of a higher incidence of confusion at one week after surgery in those patients receiving an epidural anaesthetic.

Previous clinical studies in young, trauma patients to evaluate cognitive function after long bone fractures have concentrated on patients with an associated head injury. Starr [82] concluded that early femoral fracture stabilisation did not increase the prevalence of neurological complications in patients with an associated head injury. They measured: deterioration in Glasgow Coma Scale; increase in intracranial pressure; meningism and changes on head CT scan. McKee [83] evaluated whether early intramedullary stabilisation, with its potential for cerebral embolic events, affected neurological outcome in the severely injured patient with a closed head injury. Follow up using the most sensitive aspects of neuropsychological testing (Colour Trails 1 & 2) was poor with only 30% of patients being evaluated. The conclusion using a cohort of 10 patients and no monitoring for cerebral embolic events was that cognitive function was unaffected by any cerebral (systemic) emboli produced by intramedullary fixation.

S-100B protein represents one of a range of possible markers used to quantify cerebral injury and has been correlated to the severity of brain injury [96]. Trends have previously been established between neurocognitive deterioration and increased S100B protein levels [90]. However, the specificity and sensitivity of this marker has been questioned. Contamination by extracerebral tissues either from damage or infection can produce positive results with probable origins in traumatized fat, muscle, and bone marrow [96]. Increased S100B protein levels detected following bilateral femoral fractures indicate that bone marrow may be a potential S-100B source [95]. In this present study, the median initial pre-operative levels were above the reference range and a higher concentration was measured in the more severely injured patients (multiple and open fractures) which corresponds to greater initial tissue damage (see asterisks in table 2 on

page 86). This confirms previous findings of large increases in serum S100B protein levels after extracranial injuries [96]. The rapid decline of S-100B protein levels back towards the normal reference range by 48 hours after surgery in this present study would indicate no evidence of ischaemic (secondary) cerebral injury.

Monitoring for cerebral embolic signals after intramedullary long bone fracture stabilisation is a useful method of detecting patients who have experienced high cerebral (i.e. systemic) embolic loads and who may go on to develop subsequent complications. However, the intraoperative embolic loads experienced in this present study were relatively small, infrequent and a correlation with cognitive dysfunction could not be established. In addition the usefulness of this technique is limited as it does not directly affect patient management.

The strengths of this fracture study are in the sensitivity and range of cognitive tests used which detected early changes not previously documented in young trauma patients who have sustained isolated long bone injuries. The primary aim was to establish any correlation between cognitive decline and cerebral embolic load. No further comment can be made with regards to the likely aetiology of the detected cognitive changes, other than that they appear unrelated to cerebral emboli detection. Postoperative cognitive dysfunction after surgical procedures similar to intramedullary nailing has previously been documented with the main risk factor being increasing age. However, the aetiology in younger patients is less defined with standardisation of other possible risk factors such as length of anaesthesia and the effects of analgesia difficult to achieve.

Subtle impairment of memory and mental processing speeds after trauma can delay rehabilitation and prolong hospital stay [178]. It can also have implications after hospital discharge with regard to return to work and resuming the activities of normal daily living [179]. Sensitive testing methods are available and may help target patients who require formal cognitive rehabilitation following injury. Directions for future research include monitoring for cerebral embolic events during fracture stabilisation in the presence of concomitant injuries (e.g. chest) where the risks of developing sequelae related to fat embolus are higher.

Chapter 3 Case Report: The Cognitive Effects of Fat Embolus Syndrome after an Isolated Femoral Shaft Fracture

3.1 Introduction

The neurological features of fat embolus syndrome and acute respiratory distress following trauma are thought to result from cerebral embolisation and secondary hypoxaemia [25,26]. However, the long-term cognitive effects in patients who recover from these conditions are unclear. The purpose and relevance to this thesis of the following report is to document the case of a patient who developed and recovered from fat embolus syndrome after sustaining an isolated femoral diaphysial fracture, which was stabilised by intramedullary nailing. This patient was admitted to our trauma unit prior to the commencement of the clinical fracture study documented in chapter 2. No intra-operative transcranial Doppler monitoring measurements were obtained. However, comprehensive neuropsychological testing over the subsequent eighteen months revealed significant and persistent cognitive dysfunction.

3.2 Case Report

A twenty-three year old female analytical chemist, educated to degree (Bachelor of Science) level, with no previous medical complaints, sustained an isolated transverse fracture of her right femoral diaphysis with no associated chest injury during a soccer tackle. Oxygen saturations on admission were normal at 98%. Longitudinal skin traction was applied in the emergency department to stabilise the fracture in preparation for intramedullary fixation. Six hours after admission she developed acute dyspnoea and a tachycardia and became transiently unresponsive. Oxygen saturations had fallen to 84%

on maximum oxygen therapy. She was transferred to the Intensive Care Unit where her respiratory condition deteriorated further. Arterial oxygen partial pressure (Pa O_2) was 8.3kPa with an inspired oxygen fraction (Fi O_2) of 0.6. This resulted in a PaO_2/FiO_2 ratio of 13.8. Diagnostic criteria for both acute respiratory distress and fat embolus syndrome were fulfilled [180]. The patient was intubated and required positive airways pressure ventilation (17 mmHg) to maintain her arterial oxygen saturations around 90%. The patient's respiratory status appeared well controlled with this ventilatory support and her arterial oxygen concentration was above 10kPa. The femoral fracture was stabilised using an antegrade 12mm diameter intramedullary nail (T2 system, Stryker Trauma, Geneva, Switzerland) after the canal was reamed from 9 to 13mm in 0.5 mm increments (Zimmer Intramedullary Reamers, Indiana, USA). This procedure was performed on a scheduled trauma list eighteen hours after admission. Postoperatively the patient developed widespread petechial haemorrhages and a chest radiograph confirmed diffuse pulmonary infiltrates with no evidence of cardiac failure. Subsequent bloodstained bronchoalveolar lavage samples grew methicillin sensitive Staphylococcus aureus and Haemophilus influenzae. This ventilatory-associated pneumonia was attributed to aspiration around the time of her respiratory deterioration and appropriate intravenous antibiotics were given. The patient required a 10-day period in the intensive care unit and was extubated 7 days after surgery. Four daily arterial blood gas measurements were made over this 10 day period (40 in total), with only one having an arterial oxygen concentration below 8 kPa (7.7 kPa measured on first day after surgery).

After extubation and a period of observation with continued respiratory support, which involved humidified oxygen therapy, the patient was transferred back to the trauma ward. Neurological observations were normal with no apparent confusion or cognitive problems. She was mobilised with the help of physiotherapy and discharged home.

On the day of her discharge, the patient was assessed with the range of neuropsychological tests described in Chapter 2. These included: Weschler Test of Adult Reading (WTAR) [86]; Colour Trail Making Tests parts I and II [84]; Controlled Oral Word Association Test (COWAT) [87]; Digit Span and Word List Subtests from the Weschler Memory Scale (WMS-III) [85]. These tests were performed six weeks after injury and the results are shown in Table 1. The results are expressed in percentile terms in comparison to the predicted age and intelligence matched female population.

Table 1

Cognitive tests applied six weeks following injury with results expressed as percentiles of the predicted pre-morbid cognitive score as determined by the (PFSIQ) (%)

Tests	Results (%)
Weschler Test of Adult Reading (WTAR)	**75**
Colour Trail Tests (CTT) parts I and II	**12 (I)** **<1 (II)**
Controlled Oral Word Association Test (COWAT)	**<1**
Digit Span (WMS-III)	**50**
Word Lists (WMS-III) A; D; Interference; Retention	**75; 50; 63; 63**

On the basis of the patient's age, sex and intelligence (which is based upon the results obtained on the WTAR (i.e. 75%)), it was predicted that the patient's test performances should fall within the top 25% of the population. However her performance on parts I and II of the Colour Trails Test were only at the 12th and 1st

percentiles respectively. Similarly, her performance on the COWAT was within the bottom 1%. These scores would indicate marked cognitive impairment with difficulty in performing skills that involve the frontal lobe. These include sustained and divided attention to the required tasks and poor verbal fluency.

These initial tests indicated serious cognitive dysfunction, which was then investigated with further more detailed neuropsychological assessment by a consultant clinical psychologist (Dr Lorna Torrens) at 6 and 18 months after injury.

A Hospital Anxiety and Depression Scale were used at each assessment and indicated borderline anxiety but no depression. The patient reported, "Not being up to what I was" cognitively and complained, "Things are sliding by me". She considered herself vulnerable to being "caught out" and said her memory was poor.

The more detailed cognitive screen used at 6 and 18 months after injury involved the following tests: Weschler Adult Intelligence Scale (WAIS-III) [181]; Logical Memory and Family Pictures subtests of the Weschler Memory Scale [85] (WMS-III); Stroop Colour Word Task [182]; Colour Trail Making Tests parts I and II [183]; Controlled Oral Word Association Test [87] (COWAT). A summary of each test, with a brief description and test results at 6 and 18 months are shown in table 2. Results are expressed in relative percentile terms compared with an age and sex-matched normal population.

Table 2

Description of the cognitive tests applied 6 and 18 months after injury with results expressed as percentiles of the predicted pre-morbid cognitive score

Tests	Description	6 months%	18 months%
WAIS-III	Full Scale IQ	**88**	**97**
	4 indices: Verbal Comprehension	**95**	**98**
	Working Memory	**66**	**55**
	Processing Speed	**10**	**39**
	Perceptual Organisation	**94**	**99**
WMS-III	Logical Memory (Verbal) Immediate	**63**	**91**
	Logical Memory (Verbal) Delayed	**84**	**98**
	Family Pictures (Visual) Immediate	**63**	**25**
	Family Pictures (Visual) Delayed	**63**	**36**
Stroop	Sustained and switching attention	**19**	**100**
Colour Trails	Perceptual tracking, graphomotor skills, sustained and divided attention, sequencing and self-monitoring	**I - 73** **II - 54**	**82** **58**
COWAT	Verbal initiation, self-monitoring and speed	**15**	**45**

The WAIS-III is divided into 4 parts, two of these contributing to an overall verbal IQ (verbal comprehension and working memory) and two to the performance IQ (perceptual organization and processing speed). The verbal comprehension index measures factual knowledge, word meanings, verbal reasoning and the ability to express ideas in words. It is age-resistant and is an excellent indicator of pre-morbid intelligence after trauma or with progressive brain disease. By contrast, the processing speed (performance IQ) and working memory (verbal IQ) parts of this test call upon efficient and swift information-processing skills and sound concentration. They are the indices most likely to be affected by brain injury. Perceptual organisation measures non-verbal reasoning and the (largely untimed) application of visual-spatial and visual motor skills.

The WMS III has been previously described, but was expanded to measure visual (pictures) memory recall as well as word lists (verbal). Colour Trails Tests and the COWAT were also repeated. The Stroop test [182] was used to provide a measure of attentional fatigue. It relies on the patient's ability to read words more quickly than naming colours (e.g. if the word 'red' is written in blue ink a respondent will say the word 'red' more readily than name the colour in which the word is written).

At the 6 month assessment the patient's performance on verbal comprehension and perceptual organisation indices fell within the "superior" classification or within the top 10% of the population. This is commensurate with her educational and occupational achievements. However, the working memory index score was only within the average range (being a full standard deviation below these) and her processing speed index score was only just within the "low average" classification - almost three standard deviations below. These results are therefore suggestive of a highly significant compromise working memory and processing speed.

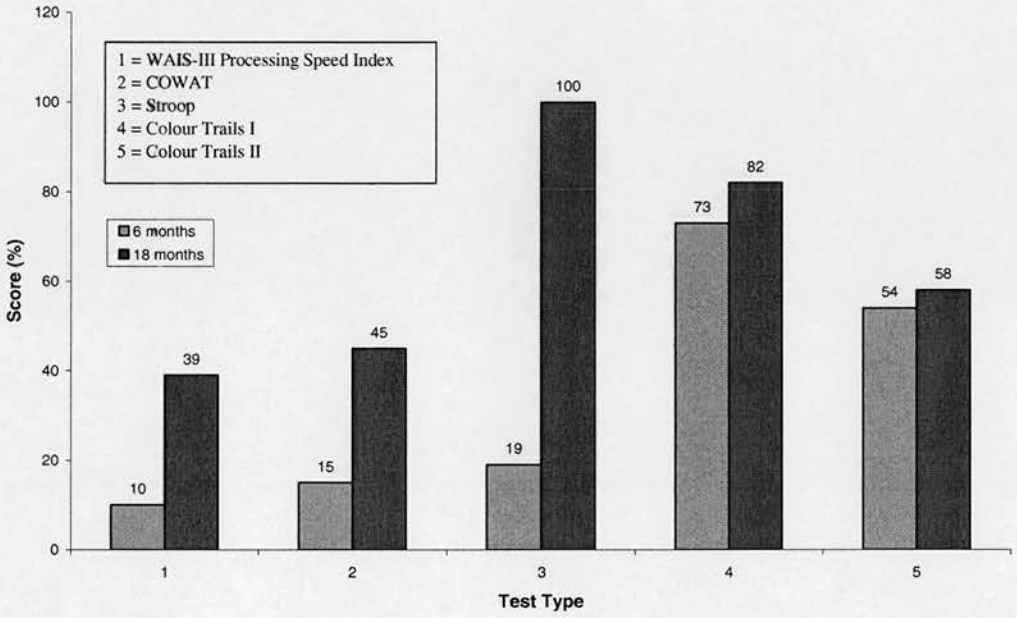
The patient's performance on the Stroop Colour Word Task placed her within the low average range for her age group, which as indicated, would indicate problems with maintaining concentration and attention. On Colour Trails I, she performed well, but was only within the average range on part II (which has increased cognitive demands). Her COWAT score had improved but was still only on the 34th percentile by comparison to her previous performance on the 1st.

By 18 months there were marked improvements in many of these areas of cognitive function. Figure 1 demonstrates the 6 and 18-month test results. The processing speed index of the WAIS-III had improved by almost 2 standard deviations.

However, performance in some areas still remained significantly poorer than would have been predicted before injury. In particular processing speed, verbal fluency and the ability to switch and divide attention at speed still remained affected. The difficulty with inhibition of automatic responses (as required by the Stroop test) appeared to have entirely resolved.

Figure 1

Summary of cognitive scores 6 and 18 months after injury. Results are expressed as percentiles of the predicted age-matched pre-morbid score.



A comprehensive cerebral MRI scan was performed six months after injury. This cerebral imaging was not performed during the patient's initial admission as the aetiology of her symptoms appeared clear and imaging would not have altered the patient's initial management. However, with the persistent cognitive dysfunction found 6 months after injury an MRI scan was performed to reveal any residual cerebral

pathology that could help explain the persistent clinical findings. This scan included T1 sagital, T2 axial, Flair axial, gradient echo T2 axial, STIR axial and diffusion weighted imaging sequences. No focal structural abnormality was found, with normal signals returned from the entire cerebrum, cerebellum and brain stem on all sequences with normal symmetrical ventricles and basal cisterns for her age. Flow in the major cerebral arterial and venous circulations was normal.

A transthoracic echocardiography was also subsequently performed with intravenous injection of agitated saline and the application of a 'Valsalva' maneuver. The patient had no evidence of any intra-cardiac or extra-cardiac right (pulmonary) to left (systemic) arterial shunting. There were 15 cardiac cycles during the Valsalva maneuver, which was applied to increase the right atrial pressure. This demonstrated no early or late shunting, which excludes an inter-atrial septal or arterio-venous pulmonary shunt.

3.3 Discussion

Specific and quantifiable defects in cognitive function were detectable using sensitive testing methods in this young patient who had made an apparent full recovery from acute fat embolus syndrome after an isolated femoral diaphyseal fracture caused by a low energy impact. The patient's original estimated intelligence quotient as measured by her PFSIQ (%) 6 weeks after injury fell within the top 25% of the population. This may be a conservative estimate and is based on a reading test alone. Her educational and occupational achievements, coupled with scores within the top 8% of the population on parts of the WAIS-III at six-month assessment would support this. The cognitive effects documented are significant with the deterioration in certain skills mimicking a typical

pattern of cerebral hypoxic injury. Specifically, verbal comprehension skills are preserved and act as an accurate indicator cognitive level prior to injury. However, skills such as working memory and speed of processing are more sensitive and susceptible to damage.

The time intervals between cognitive assessments reflect the standard practice used in cerebral injury assessment after trauma. This patient's performance on the initial tests performed 6 weeks after injury indicated serious cognitive problems. We wished to investigate this further. Comprehensive testing 6 months after injury was then performed. By that stage, one would have expected the patient to recover her cognitive function if she was going to do so. The clinical literature is consistent and suggests that cognitive performance returns to broadly normal levels during the month after a minor head injury [184]. In addition it was at around this point that the patient returned to work.

Thereafter, 18 months was the earliest point at which further cognitive testing results would not be subject to significant practice effects, which would have resulted in an improved performance. There is no consistent data on the shortest test-re-test interval that will not result in such effects using the WAIS-III. However, research with earlier Weschler scales indicated that practice effects on performance tests are minimized after an interval of 1-2 years and for verbal tests this interval is shorter [185].

Acute confusion resistant to oxygen therapy is the most common finding described in the literature in relation to cerebral fat embolisation or hypoxaemia secondary to emboli in the pulmonary micro-vasculature [25]. These effects are usually described as transient and non-specific although progression to stupor, seizures and

coma is described [186]. The long-term cognitive effects following trauma are poorly defined in the orthopaedic literature.

Prolonged arterial hypoxaemia whilst on mechanical ventilation can occur[187] and could explain the pattern of cognitive impairment seen with this patient. Transient global ischaemia after a cardiac arrest can produce similar profound cognitive defects. Memory, executive function and attentional problems have been documented, as well as the inability to return to work and pre-morbid levels of function [187-189]. However in this present report arterial oxygen concentrations appeared well maintained with only one episode below 8 kPa on arterial blood gas analysis. Persistent hypoxaemia did not appear to be a problem during the patient's time on respiratory support in the intensive care unit.

Cerebral embolic events may also have contributed to the persistent cognitive impairment. Transcranial Doppler ultrasound techniques have been used to detect embolic signals in the cerebral circulation after femoral fracture for several days following intramedullary femoral stabilisation in 5 patients with FES [34]. Unfortunately this patient did not have transcranial Doppler ultrasound monitoring of the cerebral circulation and so the cerebral embolic load before, during and after surgery was not measured. As previously discussed cognitive impairment after cardiopulmonary bypass surgery is well recognised and the reported incidence depends upon: the clinical criteria set; sensitivity of the cognitive tests used and the timing of assessment following surgery [74]. It has also been documented that the intra-operative cerebral embolic load is a main predictor of long term cognitive dysfunction after cardiac surgery and that this embolic and cognitive effect can be reduced by the use of arterial filters [68,69].

The presence of petichial haemorrhages in this present report would indicate that emboli were present in the systemic circulation. Cardiac imaging of this patient revealed no evidence of a patent foramen ovale or a pulmonary arterial-venous shunt. The relationship between a patent foramen ovale and a predisposition to the effects of systemic fat embolus has been previously established using Transoesopahgeal echocardiography [1,40]. However transpulmonary capillary passage of fat and marrow emboli can occur [39]. This may explain cerebral emboli detection in the absence of pulmonary venous to arterial shunting or a patent foramen ovale. In the previously mentioned study by Forteza[34] only one of the 5 patients with fat embolus syndrome and detectable cerebral emboli had a patent foramen ovale.

Neuropsychological impairment following acute respiratory distress syndrome has been previously documented in one study which involved 55 survivors of the condition [179]. The aetiology of this cohort was mixed with only 6 patients having sustained a traumatic injury. All patients exhibited cognitive impairment at the time of hospital discharge with 78% still exhibiting memory, attention or speed of processing problems similar to our own patient at 1 year follow up.

The enhanced imaging techniques provided by an MRI scan can aid the early clinical diagnosis of cerebral fat embolisation. Non-confluent cerebral areas and oedematous changes indicate multiple micro-emboli[11]. An MRI scan was not performed accutely in this patient and the scan performed 6 months after injury was unremarkable with no obvious cause for the patient's continued cognitive problems.

Subtle impairment of memory and mental processing speeds following trauma can delay rehabilitation and prolong hospital stay [178]. It can also have implications

following hospital discharge with regards return to work and resuming the activities of normal daily living [179]. In this individual case, the residual cognitive effects are persistent and significant. Specifically, speed of processing, working memory and attentional skills were markedly affected at the time of hospital discharge and although considerable improvements in performance were noted over the subsequent months, significant cognitive dysfunction still remains 18 months following injury. Orthopaedic and trauma surgeons should be aware of the potential neuropsychological effects of prolonged arterial hypoxemia and cerebral hypoxia caused by pulmonary and cerebral fat emboli. Referral for formal cognitive assessment may be indicated if there are any concerns of cerebral dysfunction during the follow up of such patients.

Chapter 4 Cerebral Emboli and Cognitive Function Following Elective Lower Limb Arthroplasty

4.1 Introduction

Cognitive dysfunction following emergency or elective hip arthroplasty surgery has been shown to increase complication rates and prolong hospital stay [76,190]. Cerebral emboli commonly occur during cemented lower limb arthroplasty, and can be detected using Transcranial Doppler Ultrasound techniques [35]. Cerebral embolic load has been correlated to the degree of pulmonary arterial-venous shunting [28] but the effects on clinical cognitive function remain unclear.

Sensitive neuropsychological tests are available to objectively assess cognitive function following surgery. Cerebral proteins (such as the calcium binding astroglial protein S100B protein) [90,93,96] are released into the circulation following direct cerebral trauma or embolic stroke and have been proposed as surrogate markers for neuronal injury.

The aims of this study were to accurately quantify the cognitive changes following primary cemented lower limb arthroplasty, and to assess whether these measurements correlated with the intraoperative cerebral embolic load and serum S100B protein concentration following surgery.

4.2 Patients and Methods

Fifty-one patients (mean age of 70.1 years (range = 39 to 87), undergoing elective primary cemented arthroplasty for osteoarthritis were recruited to this study. This group comprised 34 cemented total hip and 17-cemented total knee replacements. Twenty-three of the fifty-one patients were male, with a similar proportion of males in both arthroplasty groups. Exclusion criteria included a past history of cerebrovascular disease and evidence of pre-operative cognitive impairment on Mini-Mental State Examination (MMSE) defined as a score of less than 24.

A series of validated and sensitive cognitive tests were administered on the day prior to surgery. These included: Colour Trail Making Tests parts I and II [84]; Controlled Oral Word Association Test (COWAT) [87]; Mini-Mental State Examination (MMSE) [38]; Digit Span and Word List Subtests from the Weschler Memory Scale (WMS-III) [85]. These tests were repeated on the fourth post-operative day and a comparison made with the pre-operative score.

The initial 17 patients (14 total hip arthroplasties and 3 total knee arthroplasties) underwent cognitive assessment only, to establish that these tests could be successfully implemented. The following 34 patients (20 total hip arthroplasties and 14 total knee arthroplasties) underwent cognitive testing, with intraoperative transcranial Doppler ultrasound monitoring for the detection of cerebral micro-embolic signals (MES). A portable instrument (Companion III, Nicolet Biomedical Inc, Madison, USA) was used with a 2-MHz probe applied transcutaneously to locate either the left or right middle cerebral artery, as previously described in chapter 2. All the recorded signals were again analysed by two experienced technicians who were unaware of the clinical cognitive

findings (Independent Vascular Services, Wythenshawe Hospital, Manchester), using the established guidelines for cerebral embolus detection [172].

Hip arthroplasty was performed with the patient in the lateral decubitus position and the probe recording from the nondependent side. A lateral or posterior surgical approach was used to access the hip and cemented acetabular and femoral components were used (Exeter Primary V40, Stryker, Montreux, Switzerland). The procedures were carried out by a variety of different surgeons, but with 2nd and 3rd generation cementing principals applied which included pulsatile lavage, cement porosity reduction (vacuum mixing) with the use of a cement gun, pressurisation and a restrictor. Continuous monitoring was undertaken with the procedure being divided into six phases.

Phase 1 = Skin incision to removal of femoral head

Phase 2 = Acetabular preparation (reaming)

Phase 3 = Acetabular cementation and cup insertion

Phase 4 = Femoral preparation to trial reduction

Phase 5 = Femoral cementation, pressurization and stem insertion

Phase 6 = Hip relocation to wound closure

Knee arthroplasty was performed with the patient supine and the probe positioned on either the left or right temple. Primary cemented knee arthroplasty (Kinemax, Stryker, Montreux, Switzerland)) was performed through an anterior mid-line and medial parapatellar approach with intramedullary jig alignment. Pulsatile lavage was used prior to cementation of the femoral and tibial components. A thigh

tourniquet was inflated to 300mmHg prior to surgery and deflated after wound closure. Continuous intra-operative monitoring was undertaken with the procedure being divided into five phases.

Phase 1 = Surgical approach

Phase 2 = Distal femoral preparation

Phase 3 = Proximal tibial preparation

Phase 4 = Cementation, component insertion and wound closure

Phase 5 = Tourniquet release (monitoring for five minutes after deflation)

Thromboembolic prophylaxis was standardized to aspirin 150mg once daily. This was commenced one week before and continued for 6 weeks after surgery. Spinal anaesthesia with Midazolam sedation titrated at 0.5mg increments was used in 47 of the 52-arthroplasty patients, whilst the other five patients received general anaesthesia. Intra-operative monitoring included electrocardiography, pulse oximetry and non-invasive blood pressure measurements taken from the brachial artery. An intravenous morphine based patient-controlled analgesia (PCA) infusion was used until the second postoperative day with oral analgesia being subsequently administered as required for pain control.

Serum S100B protein levels were measured in all patients who underwent transcranial Doppler ultrasound monitoring. A Sangtec 100 ELISA immunosorbent assay (Diasorin Inc. Stillwater, Minnesota 55082-0285, USA) was used with blood

being collected and analysed as previously described before surgery, immediately following ('0' hours), 24 and 48 hours after surgery.

4.3 Statistical Analysis

The cognitive test scores are expressed as percentiles. A paired t-test or Wilcoxon signed-rank test was used to compare cognitive scores before and after surgery. A p-value of less than 0.05 was considered to be significant. A Mann-Whitney U test was used to compare cognitive score changes between patients who had cerebral embolic events. This was used to help determine if any changes in cognitive performance after surgery were correlated to the detection of cerebral emboli.

Scatter plot graphs and a Spearman rank correlation coefficient were also used to determine any relationship between the numbers of cerebral emboli detected, cognitive change and postoperative serum S100B protein levels.

4.4 Results

Cognitive Assessment (Total hip arthroplasties n=34; Total knee arthroplasties n=17) Tables 2 and 3 demonstrate the mean / median changes in the measured cognitive scores from pre-operative to four days after surgery in both arthroplasty cohorts. Both Colour Trails Tests have deterioration after surgery with Test 1 being statistically significant in the hip arthroplasty and Test 2 in the knee arthroplasty cohort. This indicates a significant deterioration in mental processing speed, sequencing under time pressure and sustained and divided attention. A significant deterioration in immediate memory recall was also noted in the Digit Span Subtest from the Weschler Memory Scale (WMS-III) in the knee arthroplasty cohort. The immediate recall of Word List A was seen to improve after surgery in both cohorts.

Cerebral Emboli Detection (Total hip arthroplasties n=20; Total knee arthroplasties n=14). 11 total hip arthroplasties and 5 total knee arthroplasties had detectable intraoperative cerebral emboli with a range from 1-550 and 1-24 signals respectively. The median (interquartile range) embolus count was 3 (2-16) for the hip cohort and 4 (4-20) for the knee. The distributions of these embolic signals during the different phases of each arthroplasty procedure are shown in Figures 1 and 2. During hip arthroplasty the greatest embolic load occurred with femoral cementation, pressurization and stem insertion and also on hip joint relocation. The majority of detectable cerebral emboli in the knee arthroplasty group occured in the minutes that followed tourniquet release. However, smaller loads were also detected during preparation of the distal

femur (specifically insertion of the femoral intramedullary guide) and cementation of the knee components in one patient.

One hip arthroplasty patient had a 'high' cerebral embolic load with over 500 embolic signals counted. No acute confusion was detected and this patient was discharged home six days after surgery with no detectable cognitive dysfunction. A subsequent transesophageal echocardiography revealed that this patient had a patent foramen ovale. In another hip arthroplasty patient an acute and transient period of agitation was detected intraoperatively with the patient mildly sedated under spinal anesthesia. The timing of this episode corresponded directly with the hip being relocated and a corresponding 'flurry' of detectable cerebral embolic signals. Again no deterioration was seen on cognitive testing 4 days after surgery.

Assessment of Neuronal Injury - S100B Protein Level (Total hip arthroplasties n=20; Total knee arthroplasties n=14) Serum S100B levels were measured before and at 0, 24 and 48 hours after each procedure. The median concentration before surgery was 0.15 $\mu g\ l^{-1}$ in both arthroplasty cohorts (ref range: 0.03-0.15 $\mu g\ l^{-1}$). The median (interquartile range) of S-100B protein concentrations over the four-measured time points are demonstrated in figures 3 and 4. There was an immediate peak following surgery to a median of 2.10 $\mu g\ l^{-1}$ (hip) and 1.2 $\mu g\ l^{-1}$ (knee). This concentration then fell back towards the normal reference range with median concentrations of 0.24 $\mu g\ l^{-1}$ (hip) and 0.29 $\mu g\ l^{-1}$ (knee) by 48 hours after surgery.

Comparison of Embolic Load, Cognitive Function and S100B Protein Levels (Total hip arthroplasties n=20; Total knee arthroplasties n=14) A direct comparison (Mann-Whitney U test) between cognitive test results in patients who had detectable cerebral emboli and those who did not, indicated no significant difference in any cognitive score differences in either cohort (Tables 4 and 5). This indicated that cognitive change did not appear to be directly related to embolus detection per se. Scatter plots and Spearman's rank correlations indicated no correlation between the number of cerebral embolic events and cognitive test differences.

Similar plots and calculations demonstrated no direct correlation between peak post-operative S100B protein levels and the number of cerebral embolic events or with cognitive test differences in both arthroplasty cohorts.

Table 2

A. Mean changes in the measured cognitive scores from before to 4 days after Total Hip Arthroplasty (95% confidence intervals are shown in parentheses, p values refer to the t-test results comparing differences between these paired scores, (*=p<0.05)).

	Mean change (95% C.I.)	**P-value**
Colour trails 1	-12 (-21 to -4)	0.007*
Colour trails 2	-7 (-14 to 0)	0.063
COWAT	-6 (-14 to +2)	0.125
MMSE	1 (-5 to +2)	0.363
Interference	5 (-6 to +16)	0.375

B. Median changes in the measured cognitive scores from before to 4 days after Total Hip Arthroplasty (interquartile range shown in parentheses, p values refer to the Wilcoxon signed-rank results comparing differences between these paired scores, (*=p<0.05)).

	Median change (interquartile range)	**P-value**
Digit span	0 (-12 to +12)	0.883
Word list A	12 (0 to +25)	0.002*
Word list D	0 (-9 to +13)	0.647
Retention	0 (-9 to +12)	0.864

Table 3

A. Mean changes in the measured cognitive scores from before to 4 days after Total Knee Arthroplasty (95% confidence intervals are shown in parentheses, p values refer to the t-test results comparing differences between these paired scores, (*=p<0.05)).

	Mean change (95% C.I.)	**P-value**
Colour trails 1	-18 (-38 to 2)	0.077
Colour trails 2	-18 (-28 to -7)	0.003*
COWAT	-11 (-26 to 5)	0.163
MMSE	-1 (-4 to 1)	0.258
Word list A	20 (+5 to +35)	0.012*
Word list D	-2 (-12 to 9)	0.746
Interference	0 (-14 to 13)	0.855
Retention	+1 (-9 to 11)	0.894

B. Median changes in the measured cognitive scores from before to 4 days after Total Knee Arthroplasty (interquartile range shown in parentheses, p values refer to the Wilcoxon signed-rank results comparing differences between these paired scores, (*=p<0.05)).

	Median change (interquartile range)	**P-value**
Digit span	-4 (-19 to 0)	0.012*

Figure 1

Cerebral Embolus Count and Distribution during Total Hip Arthroplasty

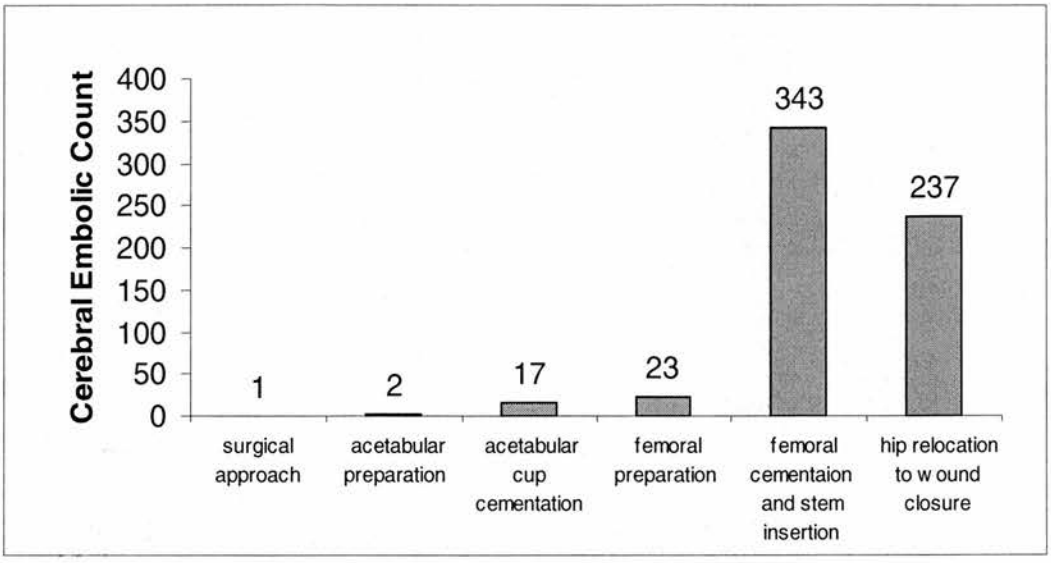


Figure 2

Cerebral Embolus Count and Distribution during Total Knee Arthroplasty

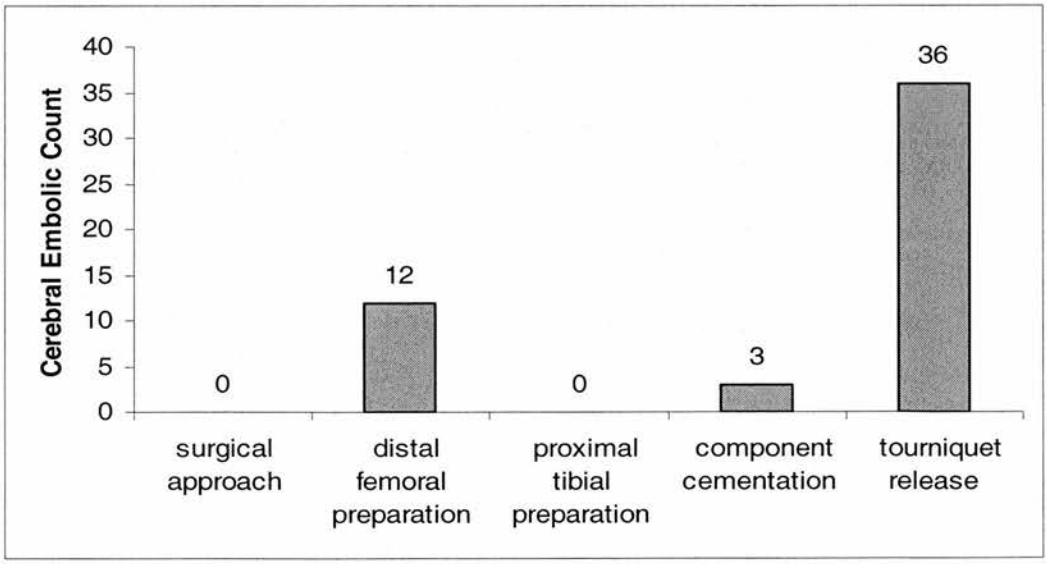


Figure 3

Median serum S100B Protein concentrations pre-operatively and at 0, 24 and 48 hours following Total Hip Arthroplasty (Interquartile Range shown between error bars)

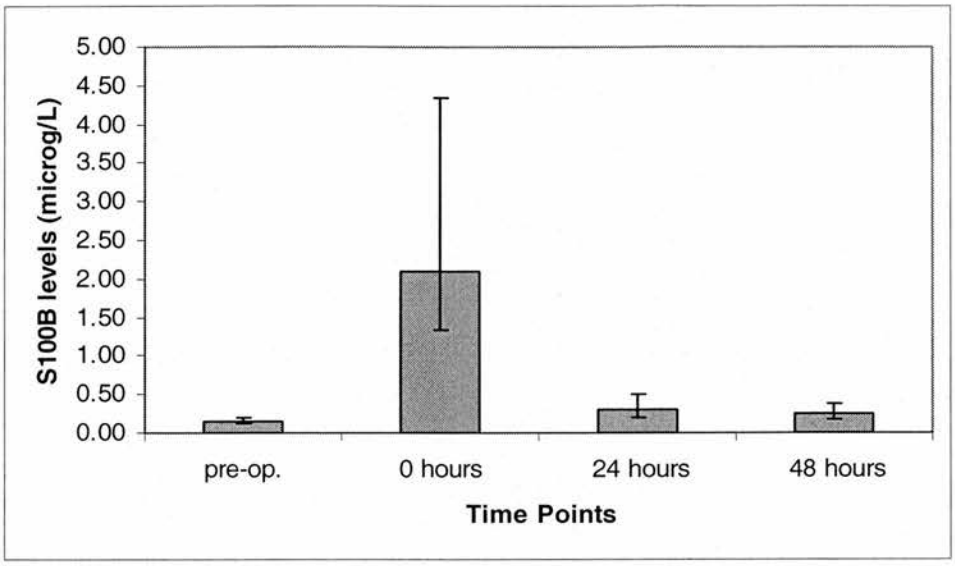


Figure 4

Median serum S100B Protein concentrations pre-operatively and at 0, 24 and 48 hours following Total Knee Arthroplasty (Interquartile Range shown between error bars)

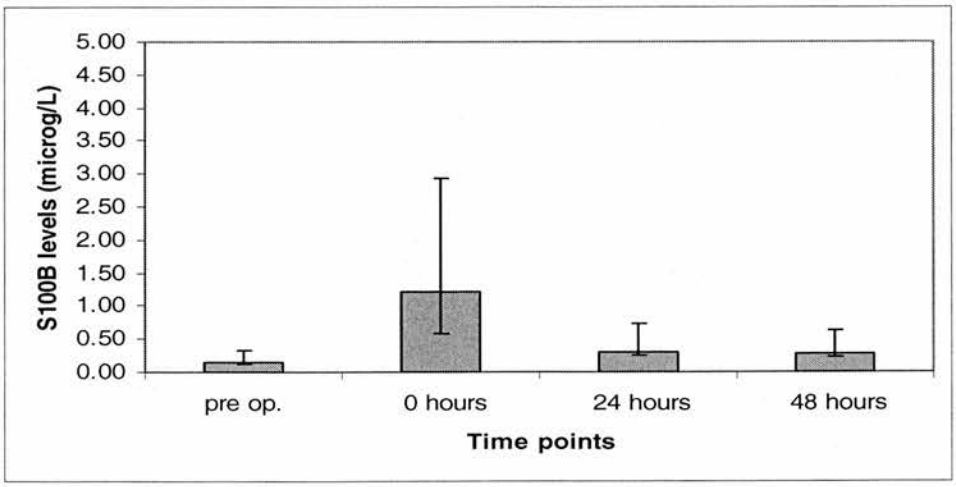


Table 4

Median difference in cognitive score changes in patients with no detectable versus detectable cerebral emboli after Total Hip Arthroplasty (interquartile ranges are shown in parentheses, p values refer to the Mann-Whitney U test comparison between both patient groups, *=p<0.05)).

	No emboli (median difference (IQR))	Emboli (median difference (IQR))	P-value
Colour trails 1	-6 (-16 to 6)	-2 (-25 to 2)	0.85
Colour trails 2	2 (-4 to 8)	-4 (-20 to 0)	0.19
COWAT	-2 (-9 to 2)	-2 (-12 to 9)	0.85
MMSE	0 (-1 to 2)	0 (-2 to 0)	0.32
Digit span	-2 (-9 to 9)	-8 (-12 to 10)	0.44
Word list A	26 (20 to 36)	13 (2 to 20)	0.08
Word list D	4 (0 to 11)	13 (-7 to 14)	0.53
Interference	12 (2 to 34)	0 (-10 to 14)	0.48
Retention	-8 (-14 to 4)	0 (-5 to 12)	0.35

Table 5

Median difference in cognitive score changes in patients with no detectable versus detectable cerebral emboli after Total Knee Arthroplasty (interquartile ranges are shown in parentheses, p values refer to the Mann-Whitney U test comparison between both patient groups, *=p<0.05)).

	No emboli (median difference (IQR))	Emboli (median difference (IQR))	P-value
Colour trails 1	-20 (-38 to -2)	-30 (-40 to -2)	0.45
Colour trails 2	-7 (-20 to -1)	-27 (-43 to -16)	0.09
COWAT	-23 (-35 to +1)	-4 (-8 to -3)	0.27
MMSE	0 (-1 to 0)	0 (-2 to 0)	0.86
Digit span	0 (-16 to 0)	-5 (-16 to 0)	0.71
Word list A	+6 (0 to +40)	+53 (+35 to +61)	0.12
Word list D	-4 (-25 to +14)	0 (-7 to +5)	0.87
Interference	+5 (-3 to +13)	-17 (-37 to +11)	0.39
Retention	-4 (-12 to +10)	+7 (+5 to +9)	0.39

4.5 Discussion

This study demonstrated an early post-operative deterioration in cognitive function, using tests, which are used to assess sustained attention, sequencing skills, perceptual tracking and mental processing speeds. These skills are thought to be subserved by the frontal lobe and test the patient's ability to monitor performance and prioritise attention to required tasks. The knee arthroplasty cohort also had a significant deterioration in early memory recall indicated by poorer digit span scores after surgery. No episodes of acute confusion were detectable using the Mini-Mental State Examination. The significant improvement documented in immediate memory recall using the word list subset of the Wechsler Memory Scale in both cohorts, was likely to be related to a practice effect owing to the lack of available parallel versions of the cognitive tests.

In 11 of the 20 hip arthroplasty and 5 of the 14 knee arthroplasty patients cerebral embolic signals were detected during surgery. The number of cerebral emboli was relatively low except in one hip arthroplasty patient who experienced over 500 detectable intraoperative emboli and had a patent foramen ovale seen on subsequent TOE. No correlation could be made between detectable changes in cognitive function and the cerebral embolic load. Cerebral embolus detection during hip arthroplasty occurred predominantly after femoral cementation, pressurization and stem insertion. In addition, hip relocation produced embolic events at the time of restoration of lower limb venous drainage. Smaller amounts of embolic material were detected during acetabular reaming, cementation and cup insertion. The cerebral embolic events during knee arthroplasty occurred predominately in the minutes following thigh tourniquet deflation,

with smaller loads detectable after intramedullary femoral reaming and alignment rod insertion for preparation of the distal femur.

The cognitive changes documented have not previously been reported in hip or knee arthroplasty patients. Acute confusion following hip fractures in the elderly population is well recognised with a reported incidence of up to 35% [75]. Risk factors showing a strong correlation to the development of confusion are age and pre-existing dementia. Three previous studies which compared cognitive function after elective hip arthroplasty and hip fracture fixation surgery have all demonstrated a reduced incidence of acute confusion in the arthroplasty cohort [79 80 81]. However the average incidence of acute confusion in these arthroplasty cohorts was still higher than this study. Duppilis [79] used the MMSE to demonstrate an 11.7% acute confusion rate following hip arthroplasty compared to 24.3% following fractured neck of femur. A similar incidence was published by Clayer [80] and Galanakis [81]. Age, pre-operative cognitive impairment, hyponatraemia, and hypoxia were correlated to the development of acute confusion after surgery.

In this study, no direct correlation could be made between changes in cognitive function and the relatively small numbers of cerebral emboli detected in both arthroplasty cohorts. Rodriguez et al [191] have recently published similar findings, with 59% of primary knee arthroplasty patients having small numbers of detectable cerebral emboli (count range 0-40) but with no direct correlation to cognitive dysfunction. Edmonds detected embolic signals in the cerebral arterial circulation in 8 out of 20 patients undergoing total hip arthroplasty [35]. Although cognitive function was not

formally assessed following surgery, no obvious neurological features were detected in any patient.

In comparison with the cardiac literature the number of cerebral embolic signals detectable is low in most arthroplasty patients. The levels required to produce a consistant clinical deterioration in cognitive function (i.e. 100-200) [68] are rarily reached. In this arthroplasty cohort one patient, with no apparent cognitive decline, only experienced a high number of cerebral emboli. This relatively high cerebral embolic load has been previously documented following lower limb arthroplasty and produced acute and transient confusion [28].

Nabavi et al [192] have established a correlation between cerebral embolic signals and the risk of embolic complications such as stroke in patients who underwent cardiac transplantation. However their detailed analysis revealed a higher negative compared to a positive predictive value. This meant patients who had lower numbers of cerebral emboli detected had a lower risk of developing clinical embolic complications. This study also suggested that a high emboli count did not directly lead to an acute stroke; rather it was an indication of a 'pro-thrombotic' state where such events were more likely. Transcranial Doppler ultrasound may therefore be better at predicting the likely risk of neurological complications after surgery rather than being used as an absolute and direct predictor.

A correlation has previously been established between cerebral (systemic) embolic load and the degree of arterio-venous pulmonary shunting [28]. Systemic embolisation following lower limb arthroplasty could be the result of either incomplete

filtering by the pulmonary microvasculature or a form of arterial to venous pulmonary shunting bypassing the pulmonary capillary bed. Paradoxical cerebral embolisation detectable using transcranial Doppler ultrasonography and the 'bubble test' has already been shown to correspond with pulmonary shunt size during primary knee arthroplasty [28]. The bubble test [28] or TOE [60] were not routinely performed in this study as the purpose was to document any clinical deterioration in cognitive function and to establish any correlation with the number of cerebral emboli. The degree of pulmonary arterio-venous shunting is a dynamic phenomenon dependant upon the pulmonary embolic load being experienced. Correlations have previously been established between intramedullary pressure, increased pulmonary embolic load and a deterioration in arterial blood gases after femoral guide-rod insertion during knee arthroplasty [64].

Koessler et al studied conventional femoral cementing techniques during hip arthroplasty and demonstrated echogenic evidence of pulmonary embolus in over 90% of cases with a demonstrable transient increase in pulmonary shunting [193]. The intensity of pulmonary echogenic events was greatest during femoral stem insertion and hip relocation. This predisposes to increased systemic embolisation during this crucial operative period where the pulmonary embolic load is high. In this present study, the femoral cementing and pressurisation period followed by hip relocation consistently produced the highest cerebral embolic loads, which corresponds to Koessler's findings of a high pulmonary embolic load during this operative period. This systemic embolic load may be exacerbated by a decrease in the pulmonary filtration capacity produced by a transient increase in arterio-venous pulmonary shunting.

Similarly, tourniquet release after knee arthroplasty can also produce substantial pulmonary embolic events. Kato [65] demonstrated a 100% incidence of pulmonary emboli visualized on transoesophageal echocardiography (TOE) after tourniquet deflation following cemented knee arthroplasty. In addition 27% demonstrated significant embolic events during femoral intramedullary reaming and alignment rod insertion. However, over 50% of patients in a subgroup with no thigh tourniquet had detectable pulmonary embolic events with corresponding hypoxaemia related to the size of the embolic load. The timing of these embolic events has been shown to last from 3-15 minutes after deflation with peak intensity at 25-45 seconds [66]. The timing of cerebral embolic signals in this present study similarly occurred in the minutes, which followed tourniquet deflation.

During cardiac surgery arterial filters have been used reduce the cerebral embolic load and have been proven to be clinically effective in reducing post operative cognitive decline [69]. In addition a sub-group of patients exhibiting 'soft' neurological signs in the non-filtered group were identified. This may lend support the concept of a broader spectrum of cognitive compromise following surgical procedures detectable only with more sensitive testing methods [36].

The S-100B protein levels demonstrated a consistent pattern of peaking immediately after surgery in both cohorts with a subsequent fall back towards the reference range. This may indicate a direct release of this substance from traumatized extracerebral tissue. No direct correlation could be made between this peak and the cerebral embolic load or on clinical cognitive decline in either arthroplasty cohort. The

S100B protein represents one of a possible range of markers for neuronal injury caused by cerebral trauma or ischemia. Extracerebral origins of this protein marker include traumatized fat and muscle, with burns, thoracic contusions and long bone fractures producing increased serum S100B levels in the absence of head injury [94]. These would appear to be the most likely sources for the increased serum levels measured in blood samples taken immediately after surgery in this arthroplasty group. The specificity of S100B protein as a direct marker of neuronal injury has been questioned due to contamination by extracerebral tissues [96]. This will produce false positive results and may be a limitation of the marker.

The primary aim of this study was to clarify cognitive function following lower limb arthroplasty and to establish any correlation with cerebral embolic load. The sensitive cognitive testing methods used detected changes not apparent with the commonly used Mini-Mental State Examination. Further comment cannot be made on the likely aetiology of the detected cognitive changes, other than they again appear unrelated to cerebral embolus detection. Post-operative cognitive dysfunction has previously been documented with the main risk factors being age and cognitive function prior to surgery.

The application of the same cognitive tests twice within one week may have caused a degree of improvement on the second test, due to a practice effect. This may have reduced the detected differences between the pre-operative and post-operative results for the tests. In addition, some confounding of our findings might have been produced by the use of two different forms of anaesthesia during surgery. However,

previous studies have shown that the pattern and magnitude of post-operative cognitive dysfunction using different forms of anaesthesia is not significant [194,195] and our use of analgesia following surgery was standardized with the use of a Patient Controlled Analgesic (PCA) regimen containing morphine. This has been shown to have little effect on cognitive function in the early stages following lower limb arthroplaty [196].

Monitoring for cerebral embolic signals during lower limb arthroplasty may be a useful method in predicting which patients are experiencing a high cerebral and therefore a systemic embolic load. However, the routine use of this technique is not justified, as it does not directly affect patient management. The poor correlation found between cognitive dysfunction and cerebral embolic load may be related to the relatively small number of cerebral embolic events detected. The cardio-thoracic literature would indicate that such a cerebral embolic load would be unlikely to produce detectable cognitive change. Directions for future research include the monitoring of bilateral arthroplasty procedures where the volume of embolisation and the incidence of post-operative confusion may be higher.

Chapter 5 Embolic, Coagulative and Inflammatory Responses to Major Trauma and Subsequent Treatment in a Large Animal (Ovine) Model

5.1 Introduction

There is substantial controversy regarding the optimal method of treating long bone fractures in seriously injured patients. Early fracture stabilisation has been shown to improve patient survival, minimise hospital stay and reduce the frequency of respiratory and systemic complications [49,66,118]. However the optimal method of fracture fixation has been debated. 'Damage Control' techniques have been proposed as a method of reducing the 'second hit' of surgery after major trauma [197]. These involve the early primary external fixation of long bone fractures instead of definitive reamed intramedullary stabilisation.

Previous animal research has examined the effects of fracture stabilisation, in a variety of canine, porcine and ovine models [41,105,136,153,154,198]. However these studies have used intact bones or surgical osteotomy, thus circumventing steps in pathophysiology caused by injury.

A large animal (ovine) model has been developed for the study of major trauma involving bilateral femoral fractures and hypovolaemia. The aim was to compare the pathophysiological responses of primary external femoral fixation and intramedullary stabilisation following injury and provide evidence as to the most appropriate surgical management.

5.2 Animals and Methods

This study was carried out at the Roslin Institute large animal centre, which is equipped with a full operating theatre and anaesthetic equipment. Collaboration was established between the Department of Orthopaedic and Trauma Surgery, and Departments of Veterinary Anaesthesia (University of Edinburgh), Intensive Care Anaesthesia (Royal Infirmary of Edinburgh), Pathology (University of Edinburgh), Medical Physics (University of Edinburgh) and Bioengineering (University of Edinburgh) during the preparation of this study. Home Office Project and Personal Licences were obtained under the Animals (Scientific Procedures) Act 1986 (PIL No 60/9678 and PPL 60/3007) prior to commencement of this project.

Twenty-four male, grey-faced sheep, aged approximately one year with a mean weight of 45.75kg (SD 5.46kg) underwent general (terminal) anaesthesia. The animals were acclimatised to laboratory housing for at least three weeks before each experiment. Twenty-four hours prior to surgery each animal was fasted, but allowed free access to water. All animals were judged to be healthy on the basis of physical examination prior to anaesthesia.

Four groups of six animals were monitored for a twenty four hour period from the induction of general anaesthesia. Group 1 (control group for anaesthesia only) underwent placement of cannulae and monitoring. Groups 2-4 (trauma groups) underwent bilateral femoral shaft fractures with a 4-hour period of subsequent untreated hypotension prior to commencement of active fluid resuscitation. At that stage Group 2 were monitored without fracture stabilisation, whilst Groups 3 and 4 underwent bilateral

femoral external fixation and reamed intramedullary fracture fixation respectively. A summary of is demonstrated in table 1.

Table 1

Summary of animal groups (1-4) with procedures performed indicated by an asterix (*)

	Anaesthesia	Trauma	Fixation
Group 1	*		
Group 2	*	*	
Group 3	*	*	External Fixator
Group 4	*	*	Intramedullary Nail

Each experiment involved a combination of anaesthetic and surgical techniques. A description of the procedures follows:

5.2.1 Anaesthesia.

General anaesthesia was induced with intravenous etomidate 0.5 mg kg^{-1} (Hypnomidate; Janssen-Cilag Ltd., High Wycombe, UK) mixed with midazolam 0.5 mg kg^{-1} (Hypnovel, Roche Products Ltd., Welwyn Garden City, UK). A cuffed endotracheal tube (Portex, SIMS Portex Ltd., Hythe, UK) sized 8.5mm-10.0mm was introduced into the trachea and connected to a ventilator circuit. Ventilation was established using a volume/pressure cycled mechanical ventilator (Nuffield 400 anaesthesia ventilator, Harlow, UK). Settings for flow, inspiratory and expiratory times were adjusted to produce visible excursions of the chest wall and peak inspiratory pressures of 30 – 40 cms H_2O at a frequency of 8 – 10 breaths $minute^{-1}$.

Anaesthesia was maintained with halothane (Rhodia Organique, Bristol, UK) delivered from a Fluotec 3 vapouriser (Cyprane, Keighley, UK). Oxygen (O_2) and nitrous oxide (N_2O) flowmeters were set at 2 and 4 l min^{-1} respectively. The inspired

and expired fractions of oxygen and carbon dioxide were monitored (Datex-Engstrom C/S3 Compact). Tidal volume was set at 600 ml and inflation pressure at 25 cms H_2O. Fresh gas flows were initially set at 1.5: 3 l min^{-1} O_2:N_2O respectively. The vaporiser setting was adjusted between 1.5 – 2.5 % on the basis of cranial nerve reflexes. Intermittent extradural or spinal anaesthesia was provided whenever haemodynamic signs, cranial nerve reflex responses or the presence of shivering indicated an inadequate "depth" of anaesthesia; a mixture of equal volumes of 2% lidocaine (Phoenix Pharma Ltd., Gloucester, UK) and 0.25% bupivacaine (Marcain Polyamp Steripack 0.25%; AstraZeneca UK Ltd., Luton) was injected. Ventilator settings and the O_2:N_2O flow ratios were adjusted to maintain Pa CO_2 values between 5.2 and 5.5 kPa, and Pa O_2 values above 13.3 kPa. After intubation and obtaining venous access, each animal received a loading dose of 3 ml kg^{-1} normal (0.9%) saline administered over a 5-minute period. A maintenance requirement of 3 ml kg^{-1} $hour^{-1}$ was then applied. An infusion controller was used throughout to administer intravenous fluids accurately.

5.2.2 Monitoring

Animals were prepared for surgery in dorsal recumbency and stabilised with props placed on either side of the thorax and abdomen. Throughout anaesthesia, heart rate and cardiac rhythm were continuously monitored using a three lead chest electrocardiogram. A central venous percutaneous sheath introducer (Arrow, PA, USA) was placed in the left internal Jugular vein using a Seldinger technique. This involved a 1-2cm longditudinal neck incision and blunt dissection down to expose the internal Jugular vein. A pulmonary artery catheter (Swan-Ganz CCOmboV, Edwards

Lifesciences, CA, USA) was passed via the sheath into the superior vena cava and advanced through the right atrium and into the right ventricle. The catheter balloon was then inflated and the catheter tip allowed to migrate into the pulmonary artery using waveform observations from the catheter tip to determine its position. The balloon was then deflated and measurements of central venous (CVP) and pulmonary arterial (PAP) pressures obtained. Values were recorded at five-second intervals. In addition a 14 guage Venflon was placed percutaneously into the contralateral jugular vein to administer intravenous fluids and allow blood samples to be withdrawn through a 3-way tap as required.

Arterial access was obtained through a 20 guage Venflon percutaneous cannulation of the external auricular artery. This allowed monitoring of systemic arterial pressure and heart rate. Arterial blood samples were obtained for blood gas measurements at hourly intervals after induction of anaesthesia and analysed (OPTI AVL Critical care analyser and Roche OPTI cassettes type E, Bio-Stat Ltd., Stockport, UK). On two occasions when access to the external auricular artery was unobtainable an arterial cannula was placed in the carotid artery using a Seldinger technique under direct vision.

All haemodynamic data were displayed on a multi-channel monitor (Datex-Engstrom Compact). Data were transferred at five-second intervals via a RS232 connection cable to a lap top computer using software designed and used under license from Datex Omeda. This allowed the recording of arterial, central venous and pulmonary arterial pressures from the Datex monitor. This was converted to ASCII format using integral software for subsequent analysis.

A suprapubic catheter was inserted to monitor urinary output. The technique used involved a 3-4cm longditudinal mid-line laparotomy incision in the suprapubic region under sterile conditions. The peritoneal cavity was incised and bladder located. A small incision (cystostomy) was made in the bladder to allow insertion of a 14G Foley catheter. The balloon was inflated and catheter secured with a purse string suture. Peritoneal and skin layers were then closed. Urine was collected in a measuring jar and output recorded at hourly intervals. Temperature was monitored continuously using a rectal probe (Helliga Servomed, Germany) and normothermia maintained.

A rumenotomy was performed in order to prevent ruminal gas accumulation that might inhibit respiration. This involved the insertion of a 9 mm cuffed endotracheal tube into the ruminal gas cap under sterile conditions after left sub-lumbar laparotomy and rumenotomy. Inflating the cuff and withdrawing the tube against the sutured margins of the incision achieved a gas and fluid-tight seal.

5.2.3 Bilateral Femoral Diaphysial Fractures

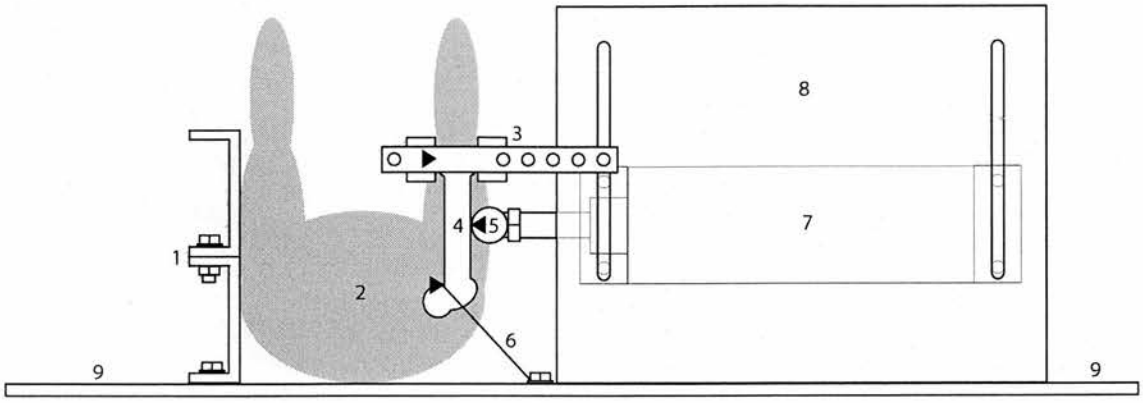
The following surgery was performed once all of the above monitoring was in place. In order to stabilise each femur prior to fracture, a 4cm longitudinal skin incision was made distally from the level of the greater trochanter. The fascia was incised and a muscle splitting approach used to expose the lateral aspect of the proximal femur. A 2.0 mm thick cable (Dall-Myles, 2.0mm, Stryker) was placed around the femur as far proximally as possible and the wound closed. The animal was re-positioned and cables secured with a single threaded screw to the actuator base plate. The distal end of the femur was secured with a clamp requiring no further soft tissue dissection. Movement of

the animal at full actuator excursion was prevented by a bracing wall positioned on the opposite side of the animal, which was also bolted to the base plate

High-energy, reproducible, closed mid-diaphysial fractures of the femur were produced using a pneumatic actuator (see figure 1). (Norgren PRA/182100/M/200, IMI Norgren Limited, Staffordshire, UK). A force of 8640N was produced using a 100mm bore cylinder and an operating pressure of 1.1MPa. The accurator was housed between 5mm thick steel plates. These were bolted onto a 12mm thick sheet steel base plate with modular threaded adjustment holes to allow attachment of devices to secure the animal. The actuator was primed and fired to produce a femoral fracture. The device was then reconfigured to produce a second fracture on the opposite hind limb. A delay of twenty minutes was required between fractures to allow repositioning of the apparatus.

Figure 1

The experimental apparatus (diagram courtesy of Mr T.O.White)



1. Bracing wall
2. Sheep
3. Knee clamp
4. Femur
5. Impact head
6. Proximal femur wire
7. Pneumatic actuator
8. Actuator housing
9. Base plate

5.2.4 Shock Period

Haemorrhage and hypovolaemia were allowed to develop spontaneously over the four-hour period, which followed fracture by withholding all but a maintenance level of IV fluid infusion. Fractures were left unstabilised during this period. The animal was left in dorsal recumbency and no attempt was made to immobilise or stabilise the fractures.

5.2.5 Resuscitation

A resuscitation protocol was instigated after this period of untreated hypovolaemia, with the primary determinants for resuscitation being mean arterial

pressure (MAP) measurement (< 60 mmHg) and hourly urine output (<1.0mL $kg^{-1}hour^{-1}$). The resuscitation protocol included increasing the fluid administration rate to 20 ml kg^{-1} $hour^{-1}$ if MAP < 60mm Hg or urine output fell to below 1.0ml kg^{-1} $hour^{1}$. If increasing the fluid regimen alone was not enough to maintain blood pressure then an adrenaline and phenylephrinine combination was administered using a dose equivalent to 100 ng kg^{-1} $minute^{-1}$ (1 in 1000 adrenaline added to a 500mls of normal saline) in order to maintain blood pressure. Metabolic acidosis (Base Excess (BE) < 2 mmol l^{-1}) was treated by giving HCO_3^- (bicarbonate) based on the equation; mmol HCO_3^- required = 0.3 x mass (kg) x BE. Each animal was continuously monitored for the 24-hour period that followed initial injury.

5.2.6 Fracture Stabilisation after Injury

After injury and four hours of untreated haemorrhage and hypovolaemia, the animals in Groups 3 and 4 underwent fracture stabilisation using external fixation or intramedullary techniques respectively.

External Fixator Stabilisation Small percutaneous incisions were made over the lateral aspect of the femur and blunt dissection used to gain access to the femoral diaphysis in order to insert 2 external fixator pins on either side of the fracture site. A single bar of adequate length was used to stabilise the fracture between the pin attachments.

Intramedullary Nail Stabilisation A 3-4cm anterior mid-line incision was made over the patella. A medial para-patellar approach was used and the patella subluxed in a lateral direction in order to gain access to the distal femur. Access to the medullary canal was gained in a retrograde fashion using a combination of bony awl and hand reamer. A

guide wire was then positioned across the fracture site into the proximal aspect of the femur. The medullary canal of the femur was then reamed over the guide wire in 0.5mm increments from 9mm to 11mm. The guide wire was exchanged and a 10mm diameter tibial nail was inserted to stabilise the fracture. Skin was sutured in an interrupted fashion.

5.2.7 Transoesophageal Echocardiography

An omniplanar transoesophageal echocardiography probe (Hewitt Packard Sonus 2000, Philips Medical Systems), obtained transcardiac images of embolic events. The images were recorded for later analysis using the integral video recorder. The probe was rotated at the level of the great vessels (approximately 55-65cm from the incisor teeth), to obtain images. Owing to the relatively spacious capacity of the sheep's oesophageal lumen a balloon was secured to the end of a 600mm length of 6mm diameter plastic tubing and secured to the back of the probe tip. This was then inflated to 100 ml using a catheter-tipped syringe, which elevated the probe tip anteriorly within the oesophagus allowing closer contact with the mucosa and clearer imaging to be established. The pulmonary root was clearly visible using this method, allowing confirmation of the pulmonary artery catheter tip position. Continuous recordings were commenced thirty seconds before and continued for three minutes after each event or until the embolic showers had disappeared completely in less than three minutes. Two observers reviewed the embolic recordings and the mean score taken.

5.2.8 Bronchoalveolar lavage

Bronchoalveolar lavage (BAL) samples were obtained by using a flexible 0.8 cm fiberoptic bronchoscope (Olympus, KeyMed, Southend-on-Sea, UK) passed through the

endotracheal tube. The bronchoscope was consistently wedged in a segment supplying a lung lobe. Three BAL samples were required per animal and each was taken from different bronchioles of a diaphragmatic lung lobe to avoid dilution effects. For lavage, sterile saline (1x50ml 0.9% NaCl) at room temperature was used and gently aspirated. The fluid was collected in a sterile container and stored on ice until subsequent analysis. Cells were pelleted by gentle centrifugation and the supernatant was removed, filtered, divided into aliquots and stored at –80°C until assayed. The cell pellet was used to calculate the total cell count from each lavage with subsequent cell differentiation and slide fixation.

5.2.9 Blood Sampling

Venous blood samples were drawn from the 14G jugular cannula and placed into two Lithium Heparin Coagulation 9 NC/3ml tubes and one EDTA KE/2.7ml tube. The EDTA was kept for Full Blood Count testing. Each coagulation sample was immediately centrifuged at 3000rpm for 10 minutes and the supernatant pipetted into 3 separate storage tubes. These were stored at –20°C until the end of each 24 hour experiment before being transferred on dry ice to a –80°C freezer. The prothrombin and activated partial prothrombin times (PT and APPT) were subsequently measured in batches. Plasma levels of fibrinogen and antithrombin III (AT III) were assayed using ELISA techniques.

5.2.10 Intramedullary Pressure and Accelerometer Measurements during Femoral Fracture

Intramedullary pressure and accelerometer readings were made on three femoral fractures. A defect in the device due to fluid contamination prevented further analysis. A

subminiature, flush diaphragm, high frequency pressure transducer (Honeywell Sensotec Sensors (model S); RDP Electronics Ltd, Wolverhampton, U.K.), with a dynamic range of ±200psi (equivalent to 13.79bar/10340mm Hg) measured intramedullary pressure during each femoral fracture.

The exposure of the proximal aspect of the femur previously described allowed adequate femoral exposure. A 3mm guide hole expanded to 8.5mm was drilled through the lateral femoral cortex to gain access to the medullary canal at the proximal metaphysial-diaphysial junction clear from the site of accurator head impact. The threaded shaft of the pressure transducer was then screwed into the femoral cortex mounting-hole and an O-ring ensured pressure sealing. An excitation voltage of 5V was used and the transducer signal amplified by a S7DC strain gauge transducer amplifier (RDP Electronics Ltd Wolverhampton, U.K.). The amplified signal was then fed into an analogue to digital converter (Pico ADC 212) before being recorded using Picoscope software onto a Pentium 4 lap top computer.

An accelerometer (model JTF, Honeywell Sensotec Sensors) with a dynamic range of ±500g was attached to the rear side of the impact head of the pneumatic actuator for continuous measurement of the level of acceleration/deceleration throughout the fracture. This also had an excitation voltage of 5V and the data were collected identically to that of the pressure transducer.

5.2.11 Euthanasia and Post Mortem Analysis

At the conclusion of each experiment, the sheep was killed with pentobarbitone 60 $mg.kg^{-1}$. Post-mortem analysis included removal and weighing of both lungs to

assess the degree of alveolar oedema. The lungs were inflated in 10% formalin and immersed in formalin for a minimum of 24 hours. 8mm thick sections were sliced and six standard, uniform tissue blocks were taken for histology, two from each of the central, apical and ventral (peripheral) aspects of each lung. Blocks were prepared for paraffin and frozen sections. Paraffin blocks were processed in a vacuum impregnating tissue processor overnight, and embedded in paraffin wax. Sections were cut on a microtome at 4 microns to be stained with Haematoxylin and Eosin. Blocks for frozen section were frozen in OCT, and cryostat sections were cut at 6 microns for the Oil Red O stains. Histological analysis was performed under light magnification. The numbers of regions containing embolic fat and bone marrow were counted in each of the standardised sections. In addition an assessment could be made of microvascular thrombosis and the presence of bronchopneumonia.

5.3 Data analysis and summary measurements of outcome

1. **Haemodynamic and metabolic response to injury:** Changes in heart rate (HR); mean arterial blood pressure (MAP); central venous pressure (CVP), mean pulmonary arterial pressure (PAP) and base excess (BE) from the time of injury to four hours following injury. In addition the immediate haemodynamic response to the first femoral fracture will be measured at 0.5, 1, 2, 5, 10 and 15 minutes after injury.
2. **Base excess and animal mortality rate:** Animal mortality was documented and the time from injury and/or fracture fixation noted. Changes in base excess (negative base deficit) from arterial blood gas analysis were documented and a median value was obtained for each of the three timeperiods of each experiment: 1. 'pre-injury'; 2. 'post-injury' (pre-resuscitation) and 3. 'post-resuscitation'
3. **Pulmonary embolic load** measured via transoesophageal echocardiography.
    a. **Femoral fracture.** This was scored using the Mayo grading system [199] which describes the size, intensity (amount) and duration of emboli visualised giving a combined score of 0-9 (this is described in table 2).
    b. **Femoral fracture fixation.** The Mayo score is limited in assessing embolic release during fracture fixation, which has duration of greater than 3 minutes. Therefore a maximum duration score would occur for all procedures regardless of the length of surgical time. In order to correct for time an average combined score of emboli size and intensity only has been calculated over each fracture fixation process to give a range from 0-6 (compared to 0-9). By multiplying this score by the mean duration of

surgery (in minutes) a new score is created which more accurately indicates the likely relative embolic load experienced over the entire fracture fixation process.

c. **Femoral diaphysial manipulation following stabilisation.** Femoral fracture sites in Groups 2-4 were gently manipulated at 2, 4, 6 and 8 hours following the start of treatment and a Mayo score calculation of embolic release made at each time point to compare the effect of fixation type. This was an attempt to mimic the clinical situation where the injured patient is transferred and moved during their initial admission.

4. **Coagulation**: prothrombin time (PTT); activated partial thromboplastin time (APTT); fibrinogen (Fib), anti-thrombin III (AT III) and platelet levels were measured from venous blood samples taken before and at 4, 12 and 24 hours after injury.
5. **Bronchoalveolar (BAL) analysis:** BAL samples were taken as described prior to femoral fracture and at 4 and 24 hours after injury. Total cell count and cell differential counts obtained (neutrophils, macrophages and lymphocytes).
6. **Pulmonary tissue histopathology**: fat and marrow emboli; intravascular coagulation +/- thrombosis; bronchitis and pneumonia. Lung weight as a measure of alveolar oedema.

A summary of the timing of the above procedures and measurements is shown in Table 3.

Table 2

Summary of Mayo Score for Pulmonary Embolic Grading

Mayo score	**0**	**1**	**2**	**3**
Intensity	None	Mild	Moderate	Severe
Duration	None	<1 minute	1-3 minutes	>3 minutes
Size	None	<2 mm	2-4 mm	>4 mm

Table 3

Timetable of Procedures

Time	Procedures
0-2 hours	Initial set up (all groups) - Intubation - Preparation (clipping / sterilisation of operative fields) - Animal transfer to operating table. - Insert central line and position Swan-Ganz catheter - Insert additional IV line and arterial line - Set up Datex monitor and attach lab-top - Supra-pubic catheter insertion - Baseline bloods and BAL taken at 1000hours
2-3 hours	Fracture preparation (groups 2-4) - Placement of Dall-Myles cables - Attachment of actuator
3-7 hours **'Shock'**	Bilateral femoral fracture (groups 2-4) - no active fluid resuscitation or fracture stabilisation - TOE imaging during each fracture - Hypovolaemia - 2nd blood and BAL samples taken at 1500 hours
7-24 hours **'Treat & Monitor'**	Resuscitation +/- fracture stabilisation and monitoring (all groups) - Ruminotomy - Intramedullary nail or external fixator stabilisation - TOE imaging throughout each stabilisation process - Fluid resuscitation protocol implemented as required - Repeat blood sampling at 2300 hours and 0800 hours (12 and 22 hours following injury) - Monitoring of cardiorespiratory data - Repeat BAL at 0900 hours
24-26 hours	Euthanasia, lung removal and lung tissue preparation (all groups)

5.4 Data Analysis

Heamodynamic readings were recorded at five second intervals and for the purposes of analysis were averaged over the following time periods in relation to the first femoral fracture (seconds): pre-fracture (-60 to -40); 30 seconds (25 to 35), 1 minute (50 to 70), 2 minutes (110 to 130), 5 minutes (290 to 310), 10 minutes (590 to 610), 15 minutes (890 to 910). A reading was also taken 4 hours after initial injury to measure the haemodynamic status of each animal before resuscitation and fracture fixation

The statistical methods described in chapter 1.6 were applied. For all analyses a p value of 0.05 or less was considered to be significant. Continuous numerical data are expressed as medians with interquartile (IQ) ranges. Mann-Whitney U tests compared measurements between group 1 (anaesthesia only) and groups 2-4 (trauma). A Wilcoxon signed-rank test was used when appropriate within groups to compare 2 individual time points. The significance of time-trends for each measurement between groups was tested using Kruskal-Wallis analysis with a pair wise comparison using a Mann-Whitney test if a statistical significance ($p<0.05$) was found.

A scatter plot was also used to establish any correlation between base excess concentrations and animal mortality

5.5 Results

5.5.1 Haemodynamic changes after injury.

The median (interquartile range) haemodynamic changes 4 hours after injury, prior to active fluid resuscitation and fracture fixations are demonstrated in Table 3. This demonstrates a significant (Mann-Whitney U test ($p<0.01$)) fall in mean arterial, central venous and pulmonary arterial pressures in the combined trauma groups 2-4 (n=18) compared to the control group 1 (n= 6, anaesthesia only), four hours after the initial femoral fracture. The median heart rate fell in both cohorts as shown over this period but not to a level which reached statistical significance.

Table 4

Median changes in haemodynamic measurements during the untreated shock period in control (n=6) and trauma (n=18) groups. (Interquartile ranges are shown in parentheses, p values refer to the Mann Whitney U test results between the unpaired scores, *=p<0.05)).

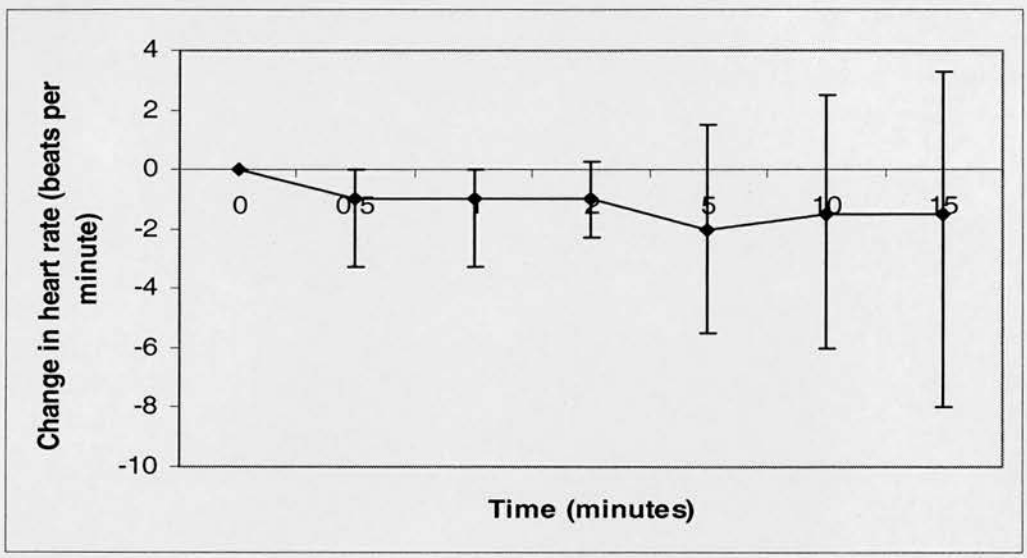
	Median (IQ)		
	Group 1 (control)	**Groups 2-4 (trauma)**	**P-Value**
Heart Rate (beats/minute)	-12 (-20 to 5)	-4 (-23 to 3)	0.790
Mean Arterial Pressure (mmHg)	-5 (-2 to -6)	-32 (-20 to -36)	0.003*
Central Venous Pressure (mmHg)	0.5 (0.0 to 1.0)	-6 (-8 to -3)	0.005*
Pulmonary Arterial Pressure (mmHg)	0 (-1 to 2)	-5 (-6 to -4)	0.003*

The immediate haemoynamic responses to injury over the first 15 minutes from the first femoral fracture are shown in Figure 2 (a-d). These figures demonstrate the initial drop in pressures (MAP, CVP and PAP) with a slight decline in heart rate.

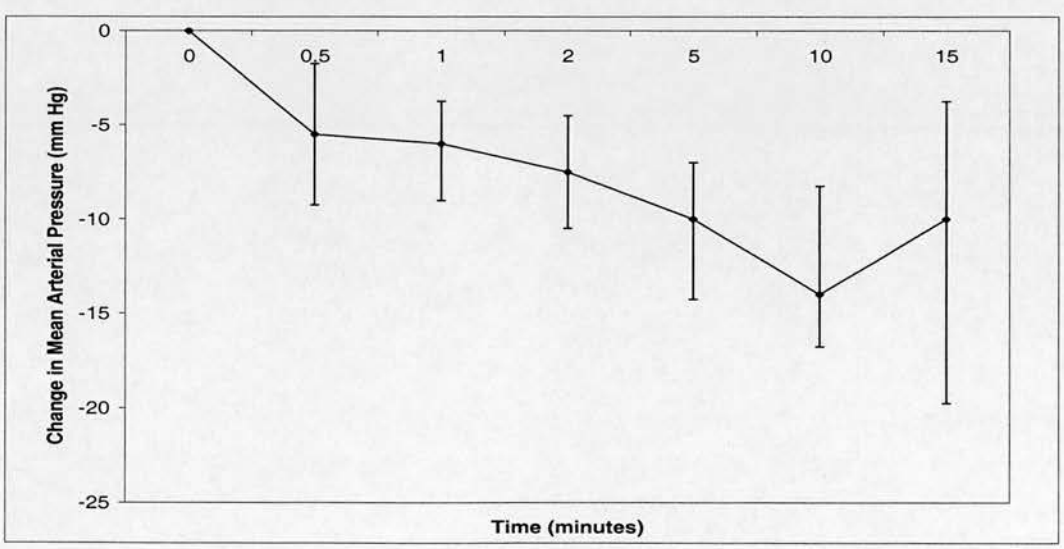
Figure 2

Median haemodynamic changes which follow femoral fracture (IQ range between error bars). a. Heart Rate b. Mean Arterial Pressure c. Central Venous Pressure d. Pulmonary Arterial Pressure

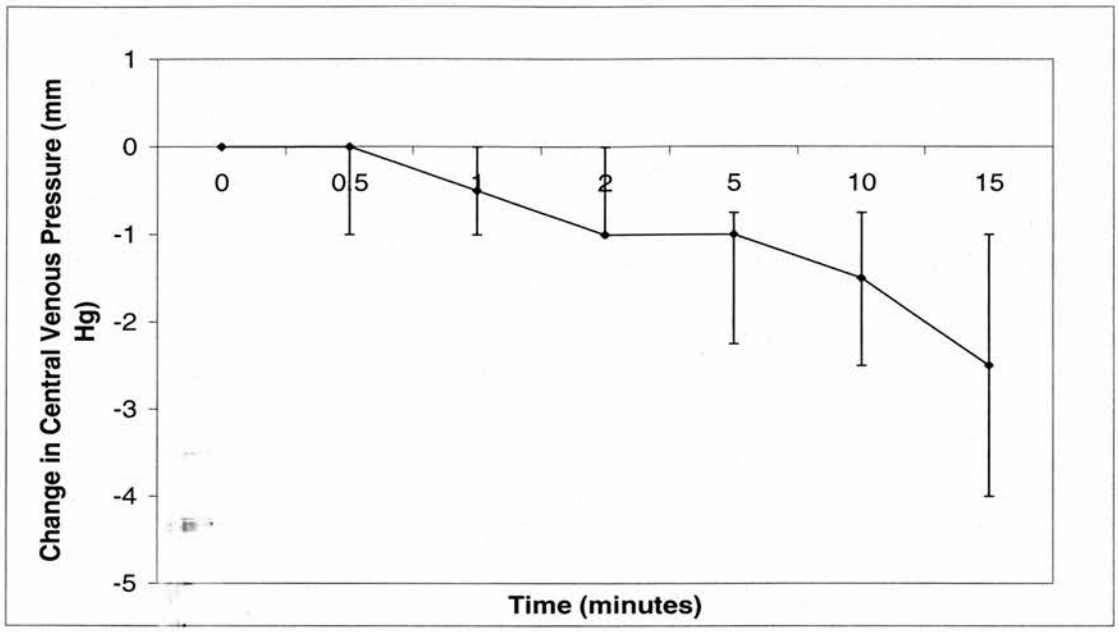
A



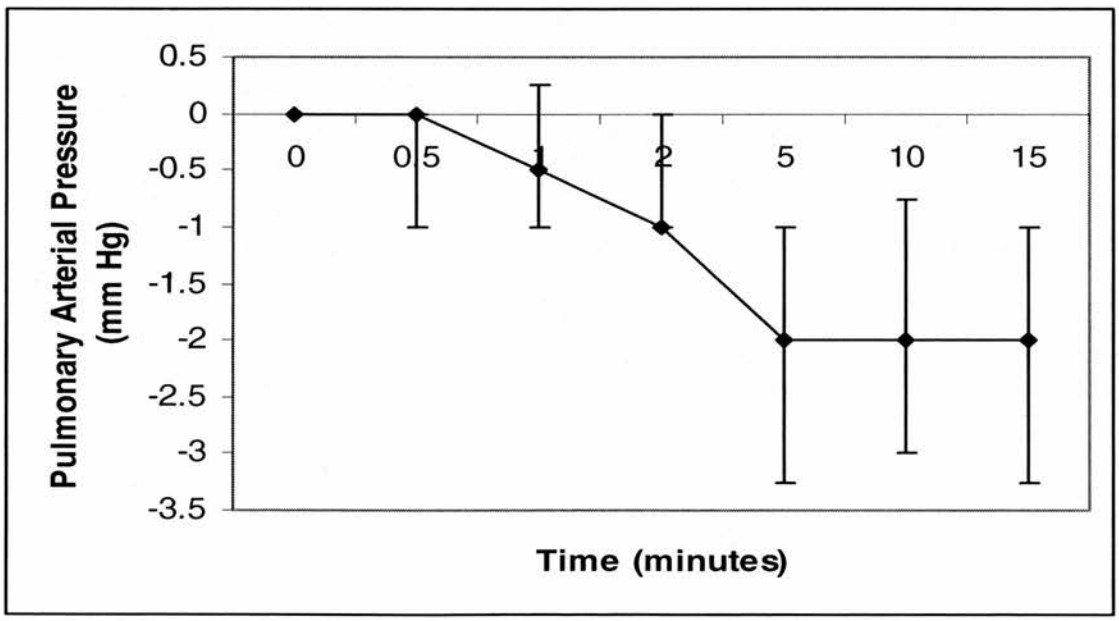
B



C


Change in Central Venous Pressure (mm Hg)
1
0
-1
-2
-3
-4
-5
0
0.5
1
2
5
10
15
Time (minutes)

D


Pulmonary Arterial Pressure (mm Hg)
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
0
0.5
1
2
5
10
15
Time (minutes)

5.5.2 Base Excess and Mortality

Three of the 24 animals tested died before the completion of the 24-hour period from anaesthetic induction at 15, 20 and 21 hours respectively. Final blood and alveolar samples were not collected from these animals. Figure 3 demonstrates the median (interquartile range) values for base excess (negative base deficit) for all hourly arterial blood samples taken over three time periods: 'pre-injury'; 'post injury' (pre-resuscitation) and 'post resuscitation' comparing control group 1 (n=6) to trauma groups 2-4 (n=18). This demonstrates a slight fall in median base excess in the control group with a rise occurring in the combined trauma group between pre-injury and post injury (pre-resuscitation) time points. However, neither change was found to be statistically significant with p-values of 0.46 and 0.67 respectively using a Wilcoxon signed-rank (non-parametric paired) test.

Over the 'post-resuscitation' phase, which included fracture fixation (groups 3 & 4) and monitoring until 24 hours after anaesthetic induction, base excess was seen to fall to median levels of 2.5 and 1.1 mmol l^{-1} in the control and combined trauma groups respectively. Individual medians for each trauma group 2-4 were 2 (fracture no fixation), 1.1 (fracture and external fixation) and 1.3 (fracture and intramedullary fixation) mmoles/L respectively for that period. Kruskal Wallis testing indicated no significant (p value=0.323) difference in median base excess concentrations between individual trauma groups over this monitoring period.

Figure 4 is a scatter plot demonstrating the correlation between median base excess/deficit values taken over the monitoring period and animal mortality. No obvious relationship can be seen between base excess concentration and mortality.

Figure 3

Median base excess (mmol l^{-1}) concentrations between control (anaesthesia only) and trauma (trauma + anaesthesia) over three time periods: pre-injury; post injury (pre-resuscitation); post resuscitation (monitoring). Interquartile ranges are demonstrated between the y-error bars.

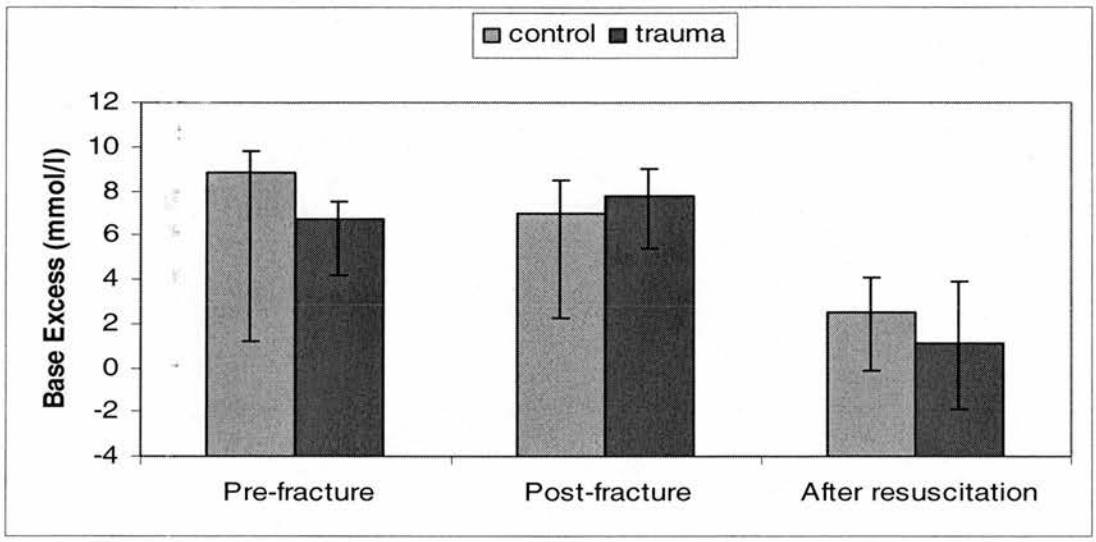
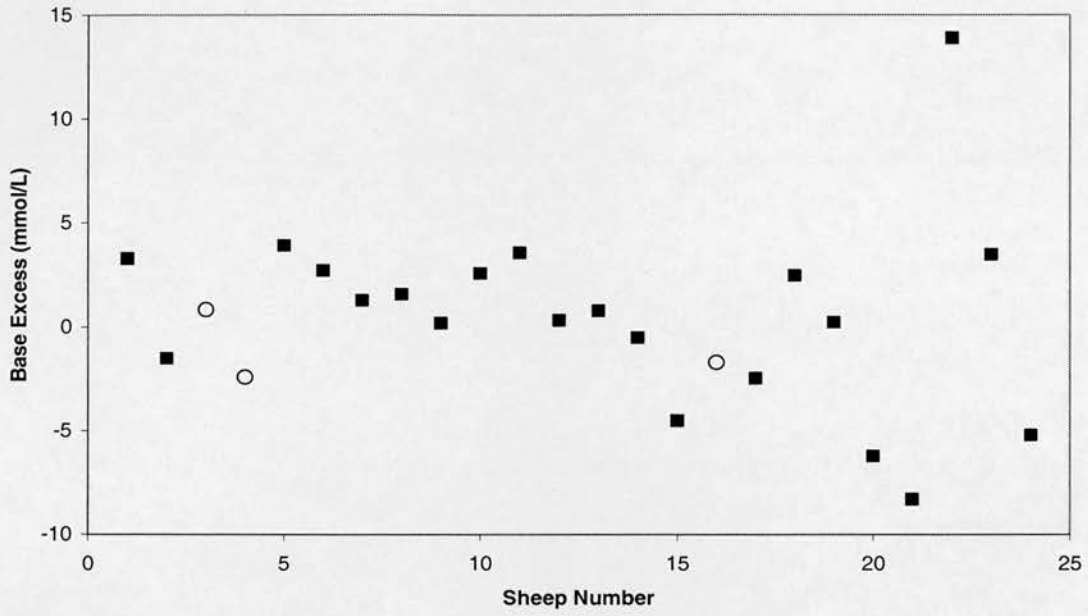


Figure 4

Median base excess (mmol/L) concentrations for all animals following commencement of IV fluid resuscitation +/- fracture fixation versus animal survival. ■ Survivors ○ Non survivors



5.5.3 Embolic Response.

a. Femoral Fracture. A median embolus (Mayo) score of 6 (interquartile range 4 to 8) was measured after each femoral fracture (n=36) with a range of scores from 3-9.

b. Fracture Fixation. The duration of surgery for external fixation (group 3) was significantly shorter (Mann-Whitney-U, $p<0.001$) per femur compared with intramedullary femoral nailing (group 4) with a median (IQ range) of 6 (5 to 7) and 10 (9 to 11) minutes respectively. The median embolic scores in terms of particle size and intensity only (i.e. modified score with a range 0-6) comparing external fixation with intramedullary stabilisation was not significantly different (Mann-Whitney-U, $p=0.06$) with median (IQ) scores of 3.5 (2.75 to 4) and 4 (4 to 4.25) respectively.

Therefore, the total embolic load (modified emboli intensity and size score multiplied by time) per femoral fracture fixation was significantly higher (Mann-Whitney-U, $p<0.001$) in the intramedullary fixation group with a median (IQ) score of 42 (32.75 to 46.25) compared with 20 (14.75 to 22.25) in the external fixation cohort. Emboli release commonly occurred during bone awl and guide-wire insertion into the femur and passing of the first reamer in the intramedullary group. However simple manipulation of the unstable fracture site during both procedures also produced an embolic response visible on echocardiography.

c. Femoral Manipulation at the Site of Fracture. Simultaneous manipulations of both femurs at the fracture site were performed in groups 2-4 (injury only, injury plus external fixation and injury plus intramedullary nailing respectively) at 4 time-points (2, 4, 6, and 8 hours) after the commencement of active fluid resuscitation +/- fracture stabilisation. The median (IQ range) Mayo score across all four time-points for groups 2-4 were 4 (3 to 5.25), 3 (3 to 4) and 3 (3 to 3) respectively. Kruskal-Wallis testing indicated that this score was significantly different across the groups ($p=0.018$). Individual group comparisons using Mann-Whitney-U testing indicated a significant ($p = 0.004$) difference only between groups 2 and 4. This indicates a higher embolic release in the unstabilised femoral fracture group compared to the intramedullary-stabilised group

5.5.4 Coagulation Marker Changes.

Figure 5 demonstrates the median (IQ range) changes in each measured coagulation marker with a descriptive summary as follows.

A. Within groups. Between time points 1 (pre-injury) and 4 (24 hours after injury):

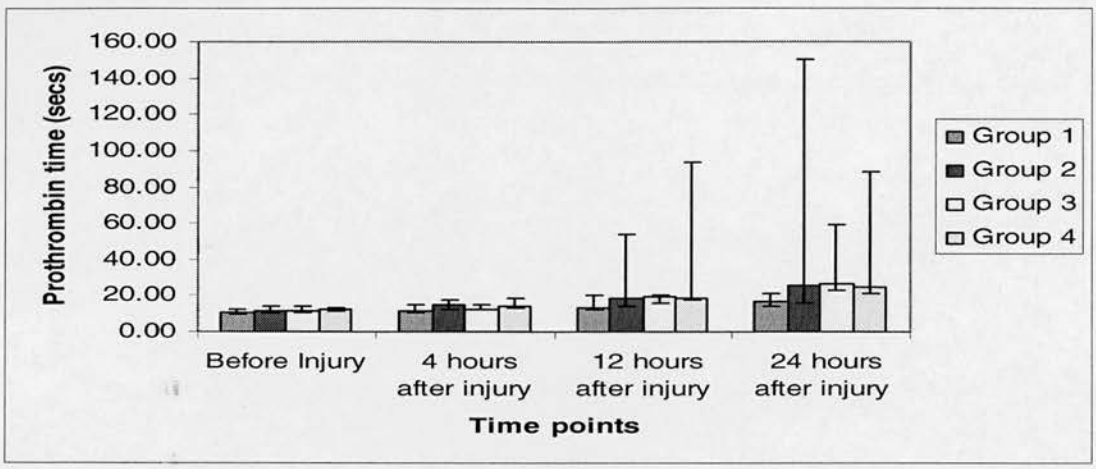
- Significant increase (Wilcoxon test, $p<0.05$) in PTT and fall in ATIII levels in all groups.
- APTT only significantly (Wilcoxon test, $p=0.028$) longer in group 2 (i.e. trauma with no fracture fixation).
- Fibrinogen levels fell significantly (Wilcoxon test, $p<0.05$) in groups 2-4 (i.e. all trauma groups).
- Platelet levels were only significantly reduced in group 3 (i.e. trauma plus external fixation (Wilcoxon test, $p=0.027$)).

B. Between groups. No significant difference (Kruskal-Wallis test) was seen between groups comparing the change in any coagulation marker between time points 1 (pre-injury) and 4 (24 hours after injury).

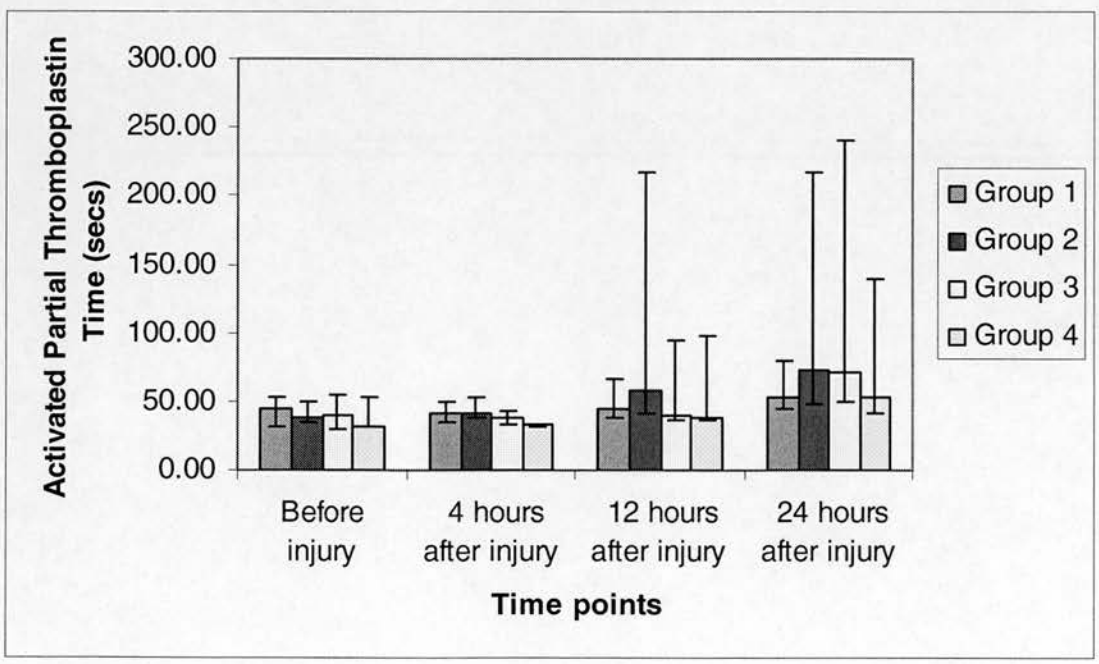
Figure 5

Median changes (IQ range between error bars) for a. prothrombin time b. activated partial thromboplastin time c. platelet count d. fibrinogen levels e. antithrombin III levels for all four groups

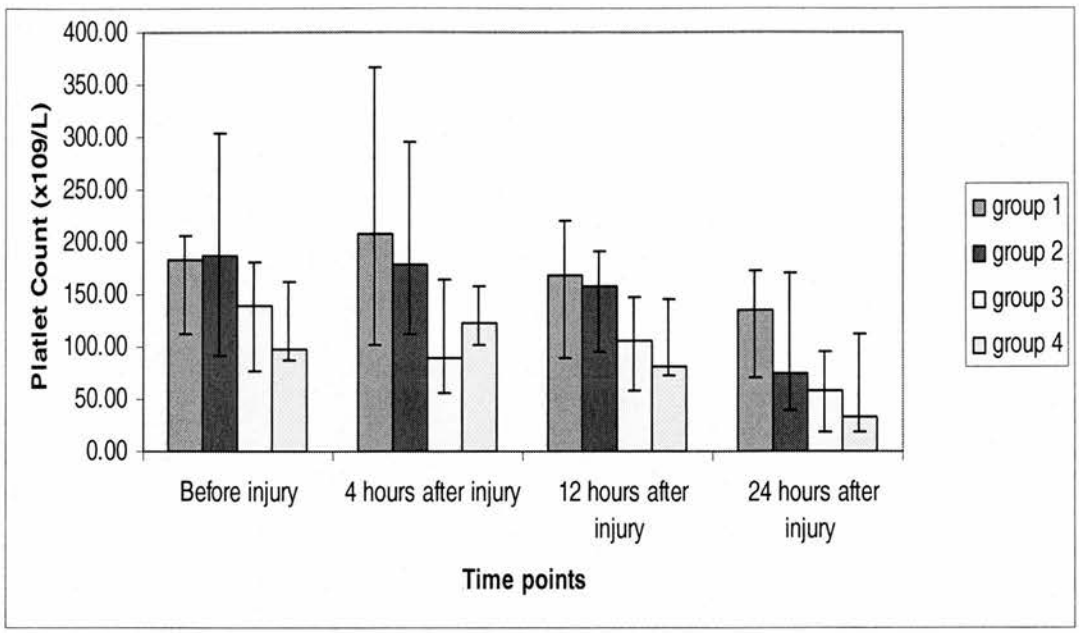
A.



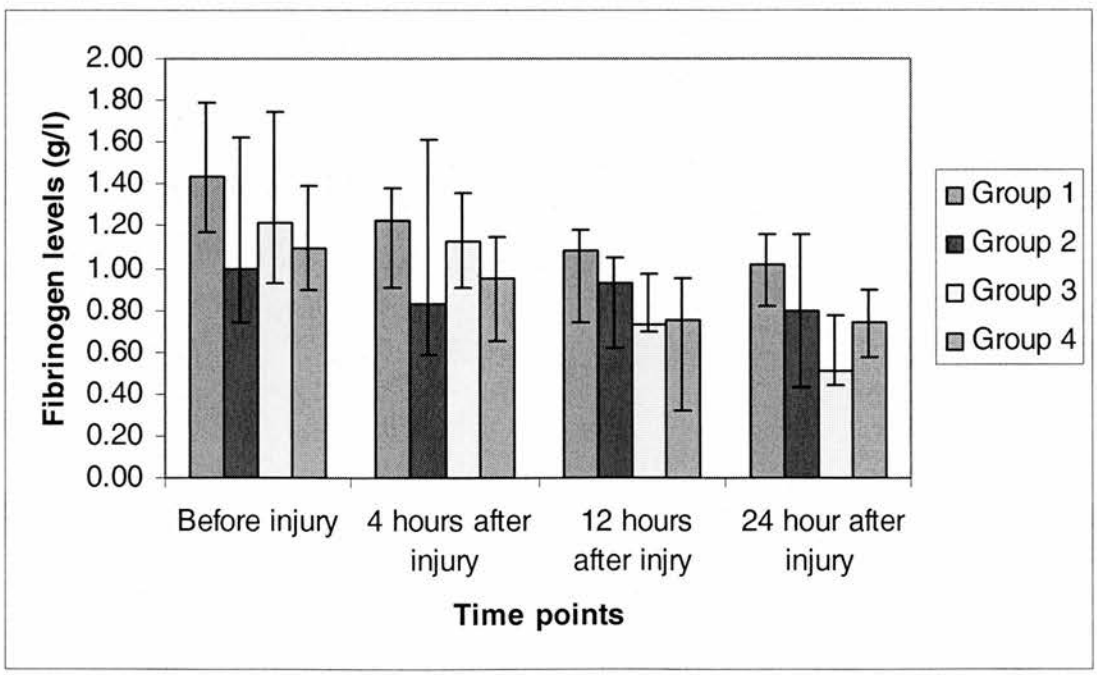
B.



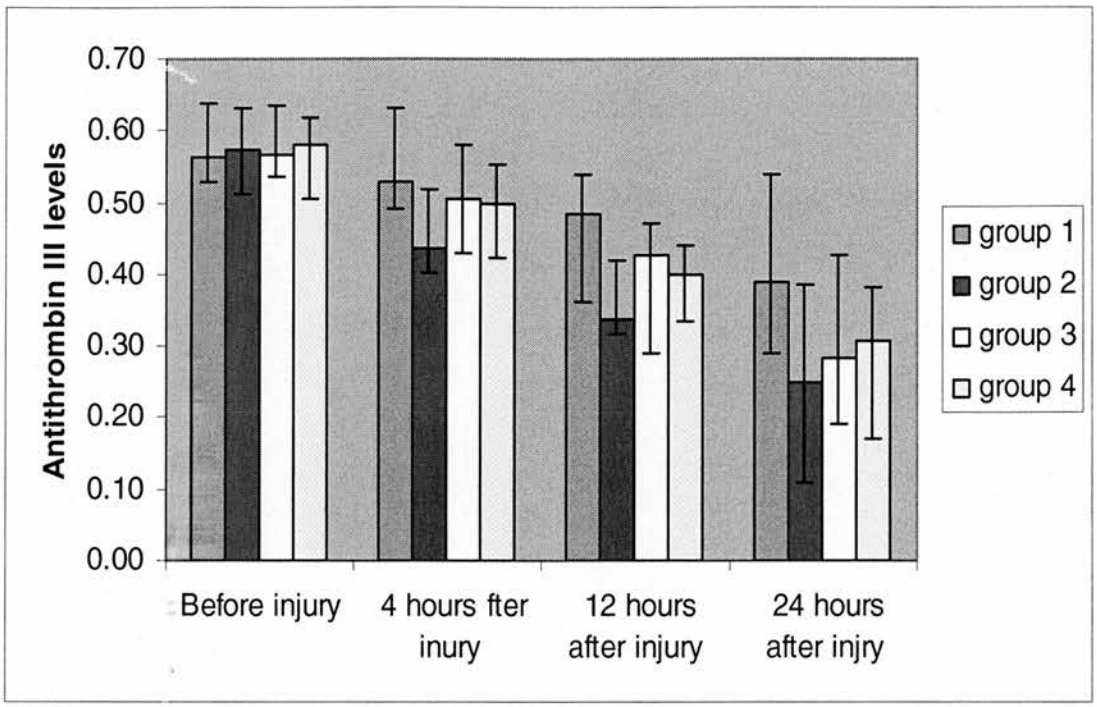
C.


400.00
350.00
300.00
250.00
200.00
150.00
100.00
50.00
0.00
Platlet Count (x109/L)
Before injury
4 hours after injury
12 hours after injury
24 hours after injury
Time points
group 1
group 2
group 3
group 4

D.


2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Fibrinogen levels (g/l)
Before injury
4 hours after injury
12 hours after injry
24 hour after injury
Time points
Group 1
Group 2
Group 3
Group 4

E.



5.5.5 Bronchoalveolar lavage

Figure 6 demonstrates the median (IQ range) changes for each lavage variable in all four groups. Three samples were taken from each animal in all groups: Before injury; 4 hours after injury (i.e. before fluid resuscitation +/- fracture fixation); 22 hours after injury. The total cell count was calculated with a cell differential count to quantify the relative neutrophil, lymphocyte and macrophage content of each lavage sample.

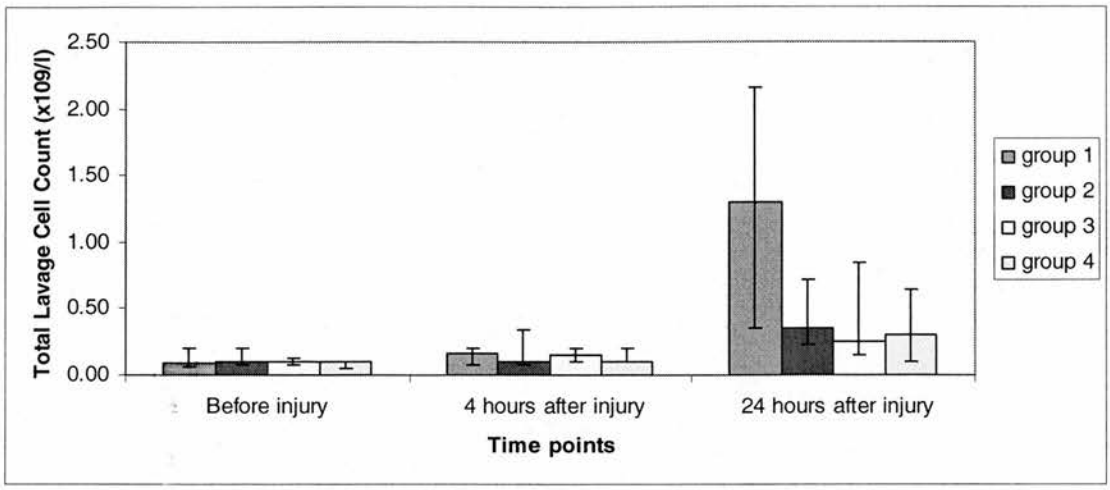
- Comparing group 1 (anaesthesia only) to groups 2-4 (trauma) there was no significant (Mann Whitney-U < 0.05) difference between any of the lavage measurements 4 hours after injury.

- By 24 hours there was a significant (Mann Whitney-U < 0.05) lower total cell count in the trauma group compared to anaesthesia only but no difference in the separate differential counts.
- Within all trauma groups there was no significant difference (Kruskal-Wallis test, p=0.21, 0.57, 0.15 and 0.81 respectively) in any lavage variable between time points 2 and 3 where the only variable was the method of fracture fixation.

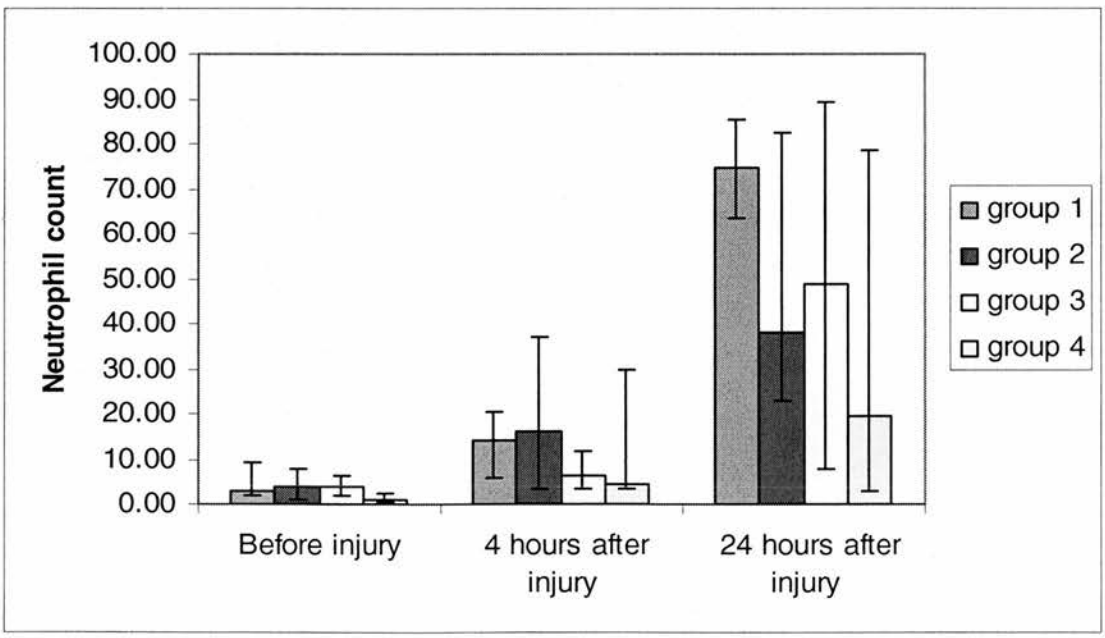
Figure 6

Median change (IQ range between error bars) for bronchoalveolar lavage measurements a. total cell count b. neutrophil count c. lymphocyte count d. macrophage counts

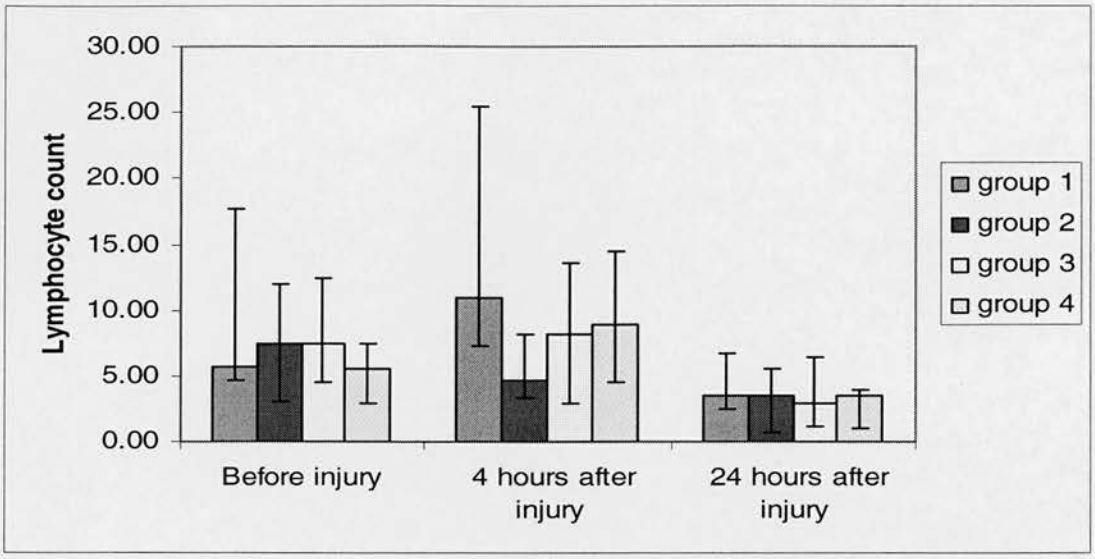
A.



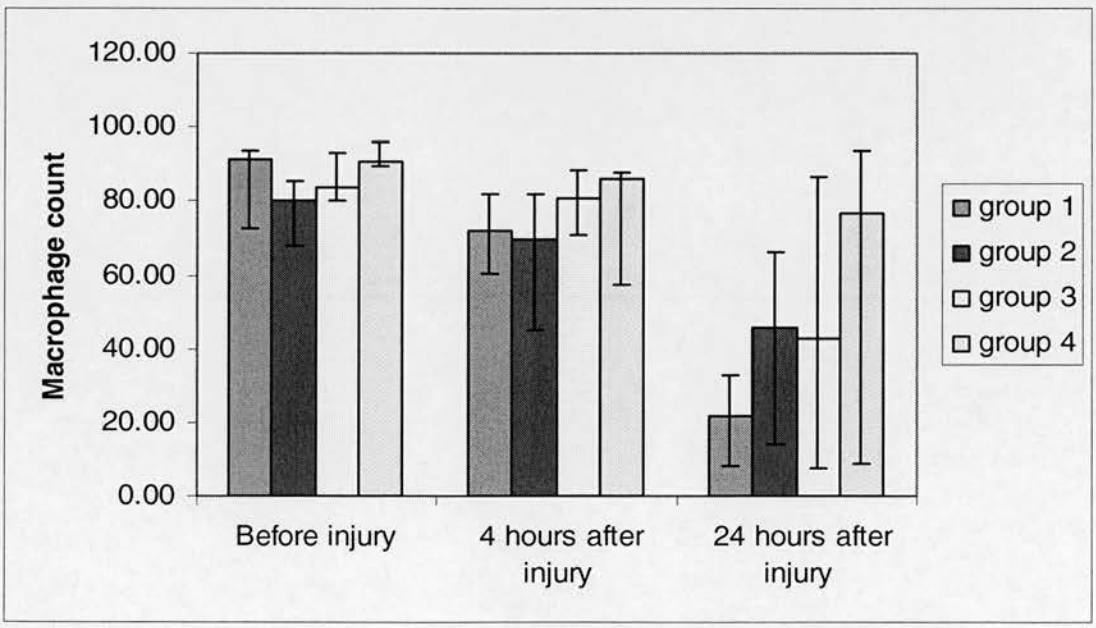
B.



C.


30.00
25.00
20.00
15.00
10.00
5.00
0.00
Lymphocyte count
Before injury
4 hours after injury
24 hours after injury
group 1
group 2
group 3
group 4

D.


120.00
100.00
80.00
60.00
40.00
20.00
0.00
Macrophage count
Before injury
4 hours after injury
24 hours after injury
group 1
group 2
group 3
group 4

5.5.6 Pulmonary tissue histopathology

a. Alveolar Oedema. The median (IQ range) lung weight, which can be used as an estimate of alveolar oedema, was 843 (736 to 898) grams in all groups with no significant difference (p=0.186, Kruskal-Wallis test) seen between groups.

b. Histopathology. The specimen results are demonstrated in Table 5. In each trauma group there was evidence of detectable fat and marrow embolus. Most sheep specimens had some evidence of infection of the bronchioles or alveoli. This had a range of severity from mild to severe. There was evidence of vascular congestion and thrombosis in each trauma group, which was graded according to the presence of thrombosis and how extensive the pattern appeared. In mild cases there was evidence of vascular congestion only, with the more severe cases exhibiting a range of thrombosis with some evidence of disseminated intravascular coagulation.

Table 5

Histopathology Results (n=6 per group)

	Fat/Marrow	Vascular congestion	Thrombosis	DIC	Bronchitis/Pneumonitis
1. Control		2			5
2. Trauma only	1	4	1	1	5
3. Trauma/Ex Fix	2	1	2	1	2
4. Trauma/IMN	1	1	3	1	3

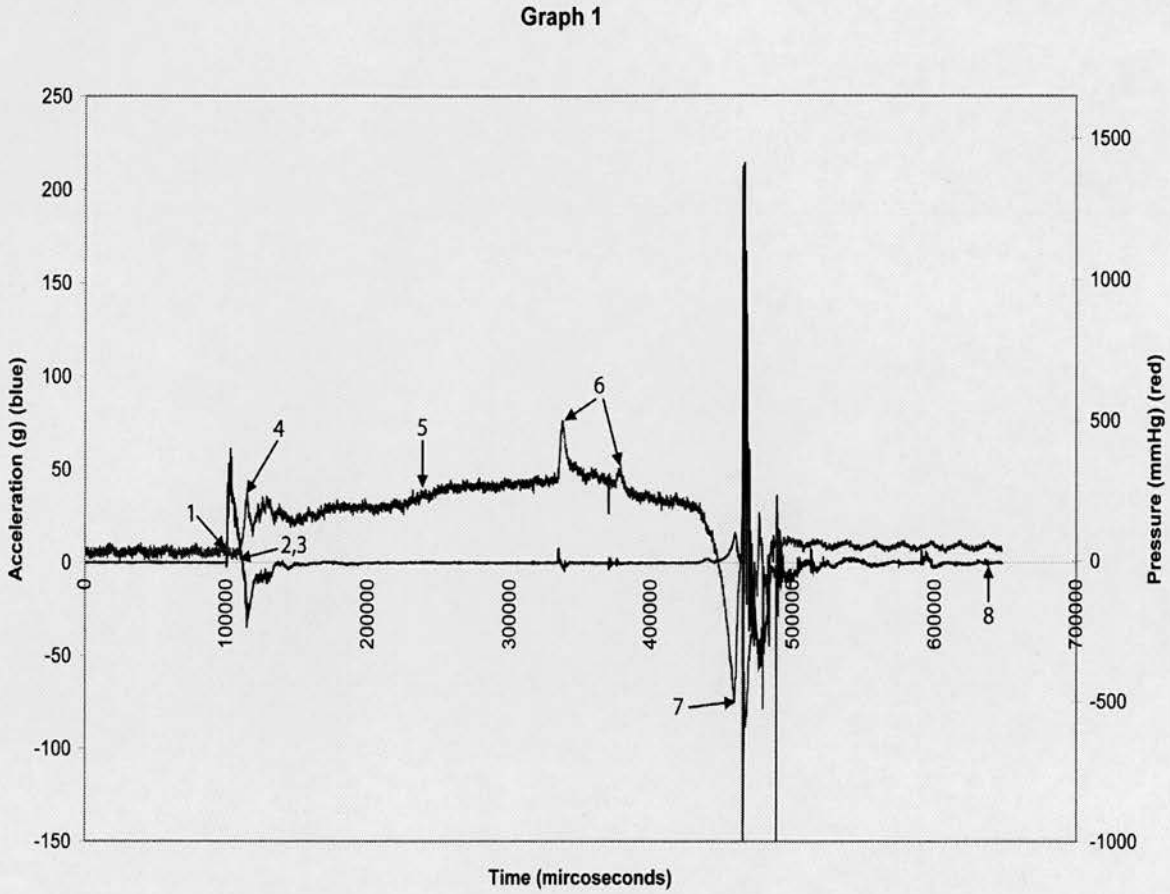
5.5.7 Intramedullary pressure during femoral fracture

Intramedullary pressure and accelerometer readings for each femoral fracture are demonstrated in Figure 7 (1-3). Resting intramedullary pressure fluctuated between 30-50 mm Hg prior to impact. On graph 7(1), the actuator is fired (1) and the impact head can be seen to have accelerated (units g = 9.8 Ns^{-2}) towards the bone and reached a maximum velocity (2) before impact. The point of impact is shown by the time at which the impact head decelerated (i.e. becomes negative) (3). This corresponded to a rise in intramedullary pressure as the femur deformed under the sudden increase in force (4). This deformation changed the volume of the intramedullary canal and the intramedullary pressure rose prior to fracture (5). During this phase, maximum pressure readings of 448, 317 and 308 mmHg were produced in graphs 1-3 respectively. Graph 1 demonstrates initial femoral diaphysial fracturing where small fluctuations in the accelerometer readings corresponded to fluctuations in pressure (6). The intramedullary cavity appeared to be intact as this correlated with an initial further increase in intramedullary pressure. In Graphs 2 and 3 these initial cracks produced a sharp fall in intramedullary pressure indicating likely intramedullary canal venting. Intramedullary pressure eventually dropped in all 3 graphs as full fracture comminution occured (7), with a corresponding brief peak in the accelerometer readings before the impact head of the accurator resumed a constant velocity (8).

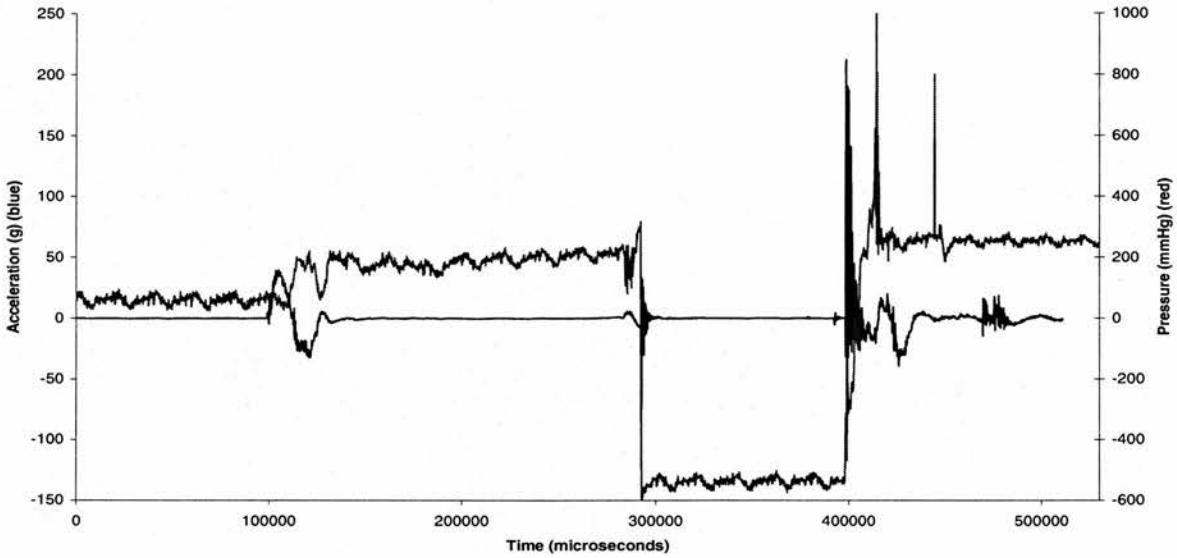
Transcardiac embolic events were recorded by echocardiography after each fracture, with Mayo grades of 6, 9 and 8 respectively.

Figure 7

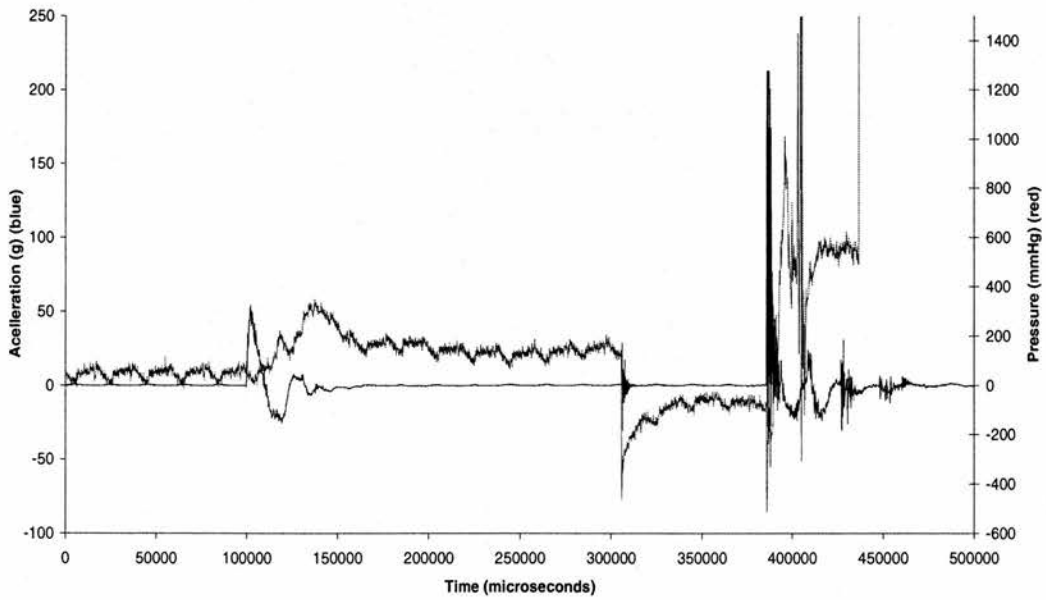
Intramedullary Pressure and Acceleration Readings during 3 Femoral Fractures (1-3)



Graph 2



Graph 3



5.6 Discussion

5.6.1 Summary of main results

The main finding of this study was that intramedullary femoral fracture fixation produced a greater pulmonary embolic load compared to external fixation. However the method of fracture fixation did not produce any measurable difference in animal morbidity or in the other metabolic, coagulative and inflammatory outcome measurements.

This large animal (ovine) trauma study involved bilateral femoral fractures with the development of hypovolaemic shock. The purpose was to mimic and better standardise a clinical situation in which the outcome of two different fracture stabilisation techniques could be compared. There were a number of outcome measurements and a brief summary of the main findings of this study is as follows:

1. An initial haemodynamic response was produced after injury in all groups with a fall in mean arterial, central venous and pulmonary arterial pressures. However, the effects of injury plus anaesthesia (combined groups 2-4) were significantly greater than the effects of anaesthetic alone (group 1) over the initial four-hour 'shock' period, which followed.
2. Base excess represents negative base deficit and is an indicator of metabolic acidosis. The effects of general anaesthetic alone (group 1) on base excess was not significantly affected by the addition of bilateral femoral fractures (combined groups 2-4) over the initial four-hour 'shock' period. Base excess levels fell in all groups as time progressed and with commencement of the intravenous fluid

resuscitation protocol. However, these levels were well maintained with the addition of bicarbonate to the intravenous fluids being administered if base excess levels fell below 2mmol l^{-1}. This may help explain the lack of correlation between median base excess concentration and animal mortality over the final 15-hour monitoring period in all animal cohorts.

3. A pulmonary embolic load was visualised on TOE and graded using the Mayo score after each femoral fracture. Intramedullary femoral fracture fixation (group 3) produced a relatively higher overall pulmonary embolic load mainly due to the longer time required for fracture stabilisation compared with external fixation. Manipulation of stabilised and unstabilised femoral fractures also produced a variable degree of pulmonary embolus during the initial hours after injury and fracture stabilisation, with significantly more embolus being visualised in the unstabilised femoral fracture group (Group 2). This has possible clinical implications with regards to patient transfer and handling during the initial phases of treatment prior to fracture stabilisation.
4. A coagulative response developed in all four groups with a significant increase in pro-thromin time (PTT) and fall in anti-thrombin III (ATIII levels). There were some differences in individual coagulation measurements within groups from before injury to the completion of monitoring at 22 hours after injury. However, the between groups comparison showed no significant differences. This indicated that the initial method of fracture fixation did not alter any changes seen with the measured coagulation criteria.

5. There were similar findings on the analysis of the bronchoalveolar lavage measurements with the combined trauma group (2-4) having a lower median total cell count by the end of monitoring but with no apparent differences seen between groups with any of the individual cell differential measurements (i.e. neutrophil, macrophage and lymphocyte).
6. Lung histopathology revealed the presence of fat emboli secondary to trauma in the pulmonary microvasculature. Intravascular coagulation was also apparent in the pulmonary microvasculature of trauma groups 2-4 with some evidence of disseminated intravascular coagulation. The high incidence of infection seen as bronchitis and pneumonitis in the fixed lung samples may make pre-operative herd infection a possibility although all animals were judged healthy on pre-operative assessment for anaesthesia.

5.6.2 Explanation of results and comparison with available literature

Haemodynamics and Metabolic Acidosis The large animal trauma model used in this study successfully produced hypovolaemia with falls in mean arterial and central venous pressures. This was as a direct result of bone and soft tissue injury, without the need for the artificial haemorrhage associated with previously published research [200]. Primarily this allowed the analysis of immediate physiological responses to injury, which is not possible in a clinical situation. These initial physiological responses have been previously described in detail by Mr Tim White (Specialist Registrar, Orthopaedics and Trauma, Edinburgh Royal Infirmary) in his MD thesis published in 2005. In this

thesis Mr White has documented an immediate parasympathetic (depressant) response on both heart rate and arterial blood pressure after injury which is attributed to the Bezold-Jarisch reflex [156]. These immediate haemodynamic responses appear to be replicated in this present study (see figure 2).

However, the primary objective of this present study was to create significant hypovolaemia from bilateral femoral fractures and the associated soft tissue damage. The haemodynamic response which develpoed during the 4-hour 'shock' period is in keeping with clinical literature regarding femoral fracture. A blood loss of up to 1.3 litres can be expected following a femoral shaft fracture [120]. Blood loss is usually higher after bilateral femoral fractures which reflects the increased severity of these injuries [121]. Blood replacement products were not available for this present animal study but transfusion requirements of up to 40% have been previously documented in the clinical literature after femoral fracture. These have been found to correlate with the preoperative degree of haemorrhage [120]. As previously stated, indirect effects of hypovolaemia include activation of platelets [45] and pro-inflammatory cytokines [123].

In this present study metabolic acidosis appeared to be well controlled with fluid resuscitation and bicarbonate administration. There appeared to be no direct correlation between animal mortality and base excess/deficit levels. The three animals that died had similar blood acidotic levels to the survivors. In addition, the method of fracture fixation in this study did not contribute to an improvement or deterioration in the ability to control base excess levels by fluid and bicarbonate administration. This may reflect the relatively small effect of fracture fixation surgery on this process and could also indicate

that blood acidotic levels were relatively stable and well controlled throughout this whole process. Clinical studies have linked poor initial blood acidotic control to increased mortality rates in injured patients with femoral fractures [129,130]. This appeared to be a time dependant relationship with a delay in acidosis correction correlating to higher mortality rates.

The Hannover group led by Pape created a large animal trauma model [105] by inducing hypovolaemia via venesection. They then allowed full haemodynamic resuscitation prior to intramedullary reaming of an intact femur. There are two main concerns using this method. Firstly, the pathophysiology of artificial haemorrhage is likely to be different from hypovolaemia produced solely from blunt trauma with bone and soft tissue damage. Secondly, by reaming an intact femur the intramedullary pressure venting that occurs from a comminuted femoral fracture is avoided. Pape [105] was however able to induce pulmonary contusion with this model thus better mimicking the group of patients that most concern advocators of 'damage control' orthopaedics (i.e. blunt chest injury requiring reamed intramedullary femoral fixation). He also created a lung lymph fistula using the technique described by Staub [201]. This involved a thoracotomy and cannulation of the efferent lymph duct leading from the caudal mediastinal lymph node. Through lymph fluid analysis it was demonstrated that intramedullary reaming directly increased pulmonary triglyceride levels and stimulated lymph polymorphonuclear lymphocytes. However, one problem with creating a lung lymph fistula is that the animal requires 48 hours to recover from the procedure.

Therefore this could not be incorporated into our animal model, which involved continuous monitoring and terminal anaesthesia.

Embolism The process of femoral fracture and subsequent stabilisation surgery performed in this study produced fat and bone marrow intravasation into the venous circulation. Transcardiac emboli entered the pulmonary circulation and were seen clearly using transoesophageal ultrasonography at the level of the pulmonary trunk. Intramedullary fracture fixation appeared to produce more embolic events primarily due to the increased length of time to perform the procedure. This correlates with the previous clinical work examining embolic phenomena during reamed intramedullary fracture fixation [1]. Schemitsch has also previously reported on the fate of intravascular fat emboli in a canine model which involved femoral intramedullary pressurisation [202]. Persistent fat emboli were seen in the small pulmonary arterioles 72 hours after injury. It has been postulated that pulmonary parenchymal damage can occur by a combination of direct mechanical obstruction and chemical destruction via lipase activation of benign fat to toxic free fatty acids [2]. However in Schemitsch's study the persistent fat emboli seen in the pulmonary tissue had induced no associated inflammatory changes. Alveolar oedema was minimal and there was scant evidence of polymorph infiltration. Therefore the contribution of the embolic events generated by intramedullary procedures to acute pulmonary inflammation after trauma was deemed negligible.

The histopathological analysis of pulmonary specimens in this present study did show the presence of fat and marrow emboli in some lung samples prepared at 24 hours

following injury in each trauma group. The method of fixation did not appear to make a difference to the frequency of fat emboli detection although the numbers of animals in each group are small. Previous work comparing plate and intramedullary fixation in osteotomised canine long bones also demonstrated no difference in the amount of persistent intravascular fat between treatment groups [203]. The relatively low detection rate of emboli in the microvasculature is likely to be due to its transient nature within the pulmonary circulation. Other factors such as the activation of coagulative and inflammatory processes may be required for persistent pulmonary tissue changes such as microthrombosis and inflammation to be seen on histopathological analysis.

The immediate effects of embolic events generated from fracture and subsequent stabilisation seem clear. Significant embolic events were seen in our trauma model immediately after femoral fracture. They were also seen during fracture fixation using both intramedullary and external fixation techniques and on manipulation of unstabilised femoral fractures. Tachakra and Riseborough have described transient hypoxaemic episodes secondary to pulmonary emboli after isolated femoral and tibial fractures without concomitant injury [10,23]. These were extremely common with an admission incidence of 64% and arterial oxygen concentrations commonly of around 60-70 mmHg. However, the majority of patients were asymptomatic. Hypoxaemia was most commonly detected after severe, high velocity injuries involving the diaphysis. These are similar to the type of fracture generated by the large animal model used in this present study.

In this present study early fracture stabilisation was seen significantly to reduce the degree of fat embolisation produced from manipulation of the femoral fractures. This mimicked the clinical situation where an injured patient is moved or transferred in the emergency department or operating room and could explain sudden hypoxaemic events which have been documented in clinical studies during manipulation and fixation of unstabilised long bone fractures [10].

The relative reduction in pulmonary embolic events by the use of initial external fixation instead of intramedullary stabilisation demonstrated might be significant in reducing the degree of hypoxaemia caused by fracture treatment. However, the clinical significance of these transient embolic events in relation to patient outcome is less clear. In the canine fat embolisation model used by Schemitsch, reaming of an intact femur produced pulmonary fat embolisation and increased pulmonary arterial pressure indicative of hypoxaemia [41]. These changes were persistent at four hours and were exacerbated by reamed intramedullary stabilisation of an osteotomised femur compared to plate stabilisation. However in both treatment groups the changes were transient and had resolved by 24 hours. The clinical significance was questioned and it was felt that fracture treatment protocol should not be altered on this basis.

However, clinical studies have linked mortality directly with the pulmonary embolic load. Christie et al demonstrated higher mortality rates in patients undergoing reamed intramedullary stabilisation of pathological long bone fractures [1]. This was attributed to the relatively greater transcardiac embolic events detected in this sub-group of patients.

In addition transcranial Doppler ultrasound monitoring could also provide an accurate and non-invasive method of monitoring the systemic (cerebral) embolic load being experienced by multiply injured patients undergoing fracture fixation.

Pulmonary arterial pressure can be used as a marker for arterial hypoxaemia. Raised pulmonary arterial pressure measurements during intramedullary fracture stabilisation are often documented in clinical and animal studies and are used as direct evidence pulmonary micro-vasculature obstruction secondary to embolic events [138]. A raised pulmonary arterial pressure indicates hypoxaemia and has been shown to be a poor prognostic indicator in the multiply injured patient [204]. However the relative contribution of additional hypovolaemia and subsequent fluid therapy to this process is unclear. In this present animal trauma model a significant fall in pulmonary arterial pressure was produced as a direct result of fracture haemorrhage with associated hypovolaemia overwhelming any direct effect of fat embolisation on pulmonary arterial pressure during fracture. Against this background of hypovolaemia there were no detectable changes in pulmonary arterial pressure during external or intramedullary fracture fixation.

Coagulation Reamed intramedullary fixation of an isolated long bone fracture has been previously shown to activate the coagulation system [138]. Similar findings to those in this present study were the prolonged activated partial thromboplastin and pro-thrombin times, with consumption of fibrinogen and platelets and an increase in thrombin degradation product levels. The method of fracture fixation had relatively little

effect on the measured coagulation variables compared to the effects of bilateral femoral fractures and shock.

Previous work has supported the concept of a synergistic embolic and coagulative response after long bone fractures with intramedullary stabilisation stimulating thrombogenic processes [108,136]. A larger embolic load secondary to intramedullary stabilisation of pathological fractures was associated with a more pronounced coagulative response and respiratory compromise (hypoxaemia). Preactivation of the coagulation system by injury may predispose to an inappropriate and severe response to thrombogenic emboli released following intramedullary procedures [138] with localised pulmonary vessel micro-thrombosis predisposing to acute lung injury.

It should also be noted that a dilutional effect due to the administration of intravenous fluids would have contributed to the drop in coagulation marker concentrations measured in this present study. Blood and plasma substitutes were not available for administration and the relative contribution of fracture fixation against a background of injury and intravenous crystalloid administration is likely to be minimal. Major trauma involving hypovolaemic shock often requires massive blood and fluid transfusion. Dilutional thrombocytopenia is not uncommon although platelet release from both the spleen and bone marrow can help compensate for this. Clinical studies have clearly demonstrated low platelet counts produced by injury and subsequent hypovolaemia [205]. These levels can continue to fall despite blood transfusion and can take several days to recover [205]. Prolonged prothrombin and activated partial thromboplastin times provide accurate indicators of the need for platelet and clotting

factor replacement, with prophylactic replacement of these products no longer standard following massive blood and fluid transfusion [206]. Evidence of disseminated intravascular coagulation and microvascular bleeding are well-recognised indicators of dilutional thrombocytopenia and the need for large dose platelet and fresh frozen plasma replacement.

Inflammation The bronchoalveolar lavage measurements made in the present study were not significantly affected by the method of femoral fixation. A significant drop in total cell count was seen in the combined trauma group (groups 2-4) compared to the effects of anaesthetic alone over the duration of each experiment. However no differences occurred with the cell differential counts, although all groups demonstrated an increased neutrophil count with time.

The majority of the lung samples in this present study had evidence of either pneumonitis or bronchitis with the presence of polymorphs visible on microscopy. The extent to which these inflammatory changes were due to the anaesthetic, embolic, hypovolaemic and coagulative processes of the previous 24-hours is difficult to ascertain. The universal nature of these pulmonary inflammatory findings across all groups in this study would indicate that our sheep cohort might have unfortunately had a respiratory infection before surgery.

Neutrophil accumulation and the release of pro-inflammatory mediators in the alveolar space have been previously shown to be a central step in the early pathogenesis of acute respiratory distress after trauma. Localised lung inflammation results in an outpouring of inflammatory exudate into the interstitial space and the integrity of the

alveolar capillary membrane can be compromised by proteolytic mechanisms. As previously indicated, Pallister has demonstrated the chemo-attractant properties of inter-leukin-8 (Il-8) which can attract neutrophils after major musculoskeletal trauma [146]. This demonstrated an important role of pro-inflammatory cytokines in enhancing neutrophil migration at the pulmonary capillary / alveolar membrane and may be an important factor in the early development of ARDS. A subsequent study by the same research group demonstrated that circulating neutrophils were primed in patients after serious injury due to changes in neutrophil surface receptor expression [207]. This resulted in an enhanced neutrophil response and subsequqent migration to Il-8, which was maintained for 72 hours after injury.

It has also been suggested that during the early phase after injury the cytokine pro-inflammatory cascade is significantly upregulated locally within the pulmonary parenchyma [144]. This can produce different patterns of concentration between pulmonary and systemic inflammatory mediators. Measurements of pro-inflammatory cytokines locally in the lung may account for lung susceptibility to an apparent generalised inflammatory response.

A recent development has been the use of inflammatory markers in the prediction of outcome following serious injury and their possible role in determining the optimal surgical strategy. Excessive systemic release of the pro-inflammatory cytokine interleukin-6 following trauma has been correlated to injury severity and patient prognosis following blunt trauma [122,140,208,209]. In addition Pape [111] demonstrated an increase in the serum concentrations of pro-inflammatory cytokines Il-6 and Il-8 in the multiply injured patient immediately following primary intramedullary femoral nailing.

These increases were not detected in patients who underwent temporary external fixation and delayed conversion to definitive intramedullary stabilisation. This group of patients seemed to react differently compared to the cohort who underwent intramedullary stabilisation during the acute 'pro-inflammatory' response phase. However, no overall difference in clinical outcome was demonstrated between treatment groups. Accurate clinical monitoring is difficult in the seriously injured patient where a decision must be made regarding the optimal method of skeletal stabilisation. Immunological evaluation may offer a more accurate method of categorising patients and determining the best form of initial long bone stabilisation. In addition it could help identify at an early stage which patients are more likely to develop acute respiratory and systemic problems secondary to their injuries.

5.6.3 Study strengths and weaknesses

The strengths of this study lie in the production of a large animal model of major trauma, which replicates the clinical situation of providing consistent femoral fractures with the associated soft tissue injury and haemorrhagic shock. This has allowed examination of the immediate physiological effects of femoral fracture as well as providing a standardised level of injury to compare fracture treatment protocols. Previous animal studies have well demonstrated neutrophil activation and raised pulmonary arterial pressure measurements following reaming of intact femurs [155,200]. Mechanically, the effect of intramedullary instrumentation of an intact long bone is different from that observed in the presence of a fracture which permits a venting effect on the pressurised intramedullary contents and the physiological responses in an

uninjured and stable animal model are also likely to be different from that existing after traumatic injury.

Monitoring under general anaesthetic over a 24-hour period had not previously been performed in an ovine model. Therefore the control group of 'anaesthetic only' was essential to determine the physiological consequences of prolonged anaesthesia and to separate those results occurring as a direct result of trauma or fracture fixation type. However an acknowledged weakness of this model is that this duration of monitoring may be insufficient to reveal pathophysiological processes, which may not occur for several days after injury such as posttraumatic respiratory insufficiency. In addition the administration of drugs such as bicarbonate and phenylephidrine were essential in some cases for animal survival and may have masked some outcome measurement differences between the four animal cohorts. From a practical and anaesthetic point of view, an even longer period of monitoring would have been difficult and likely to be beyond the animal's physiological tolerance. In addition our fracture fixations were performed as fluid resuscitation was commenced, whereas in the true clinical situation, attempted adequate resuscitation is usually performed pre-operatively with the use of blood products as required. We have also not yet been able to add blunt chest injury to our trauma model. This combined with femoral fracture would give the sub-group of seriously injured patients, which are of most interest and may provide one direction for future research using this trauma model.

5.6.4 Contribution to 'damage control' debate

The pathophysiological events that follow major trauma and subsequent treatment are not fully understood, but have implications for patient morbidity and

mortality. There is substantial controversy at present regarding the optimal method of treating seriously injured patients with associated femoral frctures. Two divergent views exist between immediate and definitive intramedullary fixation and initial external fixation with delayed conversion to an intramedullary nail once the patient's condition has been better stabilised. A lack of standardisation both with the degree of injury and treatment protocols coupled with relatively small patient numbers and differences in outcome measurements make this a difficult issue to resolve.

The clinical relevance of this study has been to quantify better the embolic and coagulative consequences of initial surgical management of femoral fractures in the seriously injured. Using transoesophageal echocardiography a lower overall pulmonary embolic load was seen with initial external fixation. The clinical relevance of this against a background of severe injury and hypovolaemia may be questioned. There was certainly no evidence that it influenced animal mortality in this study. However complications of trauma such as acute respiratory distress are often discussed in terms of reaching 'thresholds' from which end-organ damage occurs with direct links established to the severity of injury [150]. Therefore it would make sense to use any method available to reduce the 'second hit' of surgery and reduce the likelihood of such a threshold being reached and irreversible end-organ damage being produced. Initial external fixation is an acceptable alternative to immediate intramedullary stabilisation with the literature indicating that delayed conversion to definitive stabilisation can be reasonably performed once the patients condition has been optimised without increasing complication and morbidity rates [210].

Advocates of 'early total care' would argue that the degree of initial injury alone is the sole contributing factor to patient prognosis and that adequately resuscitated patients should undergo immediate intramedullary fixation [118,119,211]. Centres, which advocate 'Damage Control' techniques emphasise that an accurate assessment using inflammatory and coagulative markers, are necessary to decide on optimal initial surgical treatment and minimise the risk of respiratory and systemic complications.

It would appear from the current literature that there is some support for 'damage control' surgery on peripheral limb injuries with differences in pulmonary embolic load and inflammatory (Il-6) responses being produced by the two different surgical strategies. However improved clinical outcome in terms of patient mortality would appear to be more closely linked to the degree of initial injury and to adequate patient resuscitation. Pre-operative factors such as correcting metabolic acidosis and avoiding 'occult hypoperfusion' would appear to have a more direct link to patient mortality.

5.6.5 Intramedullary pressure during femoral fracture

A substantial rise in intramedullary canal pressure prior to femoral diaphysial fracture and subsequent canal venting was demonstrated in the three monitored femoral fractures. A correlation was established with accelerometer readings documenting the fracture process with a substantial pulmonary embolic load recorded on transcardiac ultrasound during each femoral fracture.

Intramedullary pressure changes are thought to contribute to the intravasation of fat and marrow emboli into the venous circulation after femoral fracture. The pressures recorded during the fracture process are comparable to a previous study demonstrating

pulmonary emboli after intramedullary fracture fixation [42]. Other studies have concentrated on the type and timing of fracture stabilisation in order to minimise post-operative pulmonary complications in the seriously injured [100,110,211]. Studies involving intramedullary stabilisation techniques have demonstrated substantial increases in intramedullary canal pressure. Mousavi [42] demonstrated significant pulmonary emboli during femoral instrumentation and canal preparation. Intramedullary pressure measurements were recorded using a piezoelectric gauge with values ranging from 320-1079 mm Hg. The first pass of the intramedullary reamer produced the highest-pressure changes and corresponding embolic response. Wenda et al [212] demonstrated that intramedullary pressure increases of 50mm Hg produced a 'snow flurry' of embolus detectable on transcardiac echocardiography. Higher pressures of around 200mm Hg produced a more configured embolic pattern with a thrombotic component. Reaming was also demonstrated to produce a pressure increase above 200mm Hg with corresponding emboli. Gentle manipulation of the fracture site produced an intramedullary pressure of 90mm Hg with a corresponding less defined emboli pattern visualized. This may again help explain hypoxaemic events previously documented during the closed reduction of long bone fractures [10].

This study is the first to accurately measure intramedullary pressure during high-energy femoral fractures in a large animal model replicating the clinical situation. As stated many would argue that the degree of initial injury alone (i.e. the 'first hit) is the main contributing factor to patient prognosis and that reducing the 'second hit' of surgery in terms of fracture stabilisation has minimal effect. The clinical relevance is

therefore to help quantify the initial pulmonary embolic events related to the initial injury.

Chapter 6 Conclusions and Future Research

6.1 Conclusions

The hypothesis of this thesis was that elective and emergency orthopaedic procedures produce quantifiable embolic, coagulative and inflammatory changes. Specifically the clinical studies aimed to quantify better the cerebral (i.e. systemic) embolic load and to establish any correlation with clinical outcome measurements in the form of sensitive cognitive tests, which are not routinely applied in these patients. The large animal study aimed to demonstrate the relative effect of two different fracture stabilisation strategies on mortality and various physiological outcome measurements after a standardised severe injury.

The conclusions in relation to the main hypothesis were that fracture stabilisation and joint arthroplasty **do** produce significant pulmonary and systemic embolic events, with coagulative changes seen in the animal work and early cognitive dysfunction documented in both clinical studies. Any proposed change in surgical technique which helps reduce embolic load and the physiological response to surgery does have potential and quantifiable benefits.

However the consequences of reducing pulmonary and cerebral embolic load in terms of improved patient morbidity and mortality were not established. A poor correlation was made between documented cognitive change and cerebral embolic load in both the fracture and arthroplasty patient cohorts. In addition the reduction in pulmonary embolic load produced by changing the type of initial femoral fracture fixation from intramedullary to external fixation was not reflected in improvements in

the other outcome measurements - animal mortality, blood biochemistry, coagulation and pulmonary inflammation.

6.2 Future Research

The planned areas for future research include the possible addition of chest injury to the large animal model. This would allow the investigation of the effects of femoral fracture stabilisation against a background of direct localised pulmonary injury and inflammation. Mr Colin Howie (FRCS, Consultant Orthopaedic Surgeon, Edinburgh), has also obtained ethical approval for a clinical study to compare the cerebral embolic load in patients undergoing computer assisted ('navigation') knee arthroplasty. Such surgery avoids conventional intramedullary jig alignment and has been proposed to improve anatomical alignment and functional outcome. However it has expense and training implications that have caused concern in the orthopaedic community. A reduction in pulmonary and systemic embolic load by minimising the intramedullary canal disturbance may be an additional potential benefit of computer assisted knee arthroplasty surgery. In addition the concerns over increased confusion rates and cerebral fat embolic events after bilateral knee arthroplasty could be investigated further using the available transcranial Doppler ultrasound.

Presentations, Publications and Prizes

1. Embolic, Coagulative and Inflammatory Responses to Major Trauma and Subsequent Treatment

AC Gray, TO White, E Clutton, B Hawes, J Christie, CM Robinson

Panceltic Orthopaedic Meeting	June 2006	Podium
British Orthopaedic Assn. Annual Congress	Sept. 2005	*Podium x 2
British Orthopaedic Research Society (BORS)	July 2005	Poster
(2nd prize in poster competition)		
E.F.O.R.T. Lisbon	June 2005	Podium

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**** Abstracts to be published in Journal of Bone and Joint Surgery (B)***

2. Cerebral Emboli and Cognitive Function Following Long Bone Fractures and Intramedullary Stabilisation

AC Gray, L Torrens, J Christie, C Graham, CM Robinson

AAOS annual meeting	March 2006	*Podium
Orthopaedic Trauma Association	Oct. 2005	*Poster & Podium
British Orthopaedic Research Society	July 2005	*Podium
E.F.O.R.T. Lisbon	June 2005	Podium

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Abstracts to be published in Journal of Bone and Joint Surgery

3. Cognitive Function and Cerebral Micro-emboli following lower Limb Arthroplasty

AC Gray, L Torrens, J Christie, C Howie, A Shetty, CM Robinson

British Hip Society 2005	March 2005	Poster
E.F.O.R.T. Lisbon	June 2005	Poster
Roy Petrie memorial research meeting	May 2005	Podium

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